Southern Medical Journal

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Fifty-Fifth Annual Meeting, November 6-9, 1961, Dallas, Texas

SEPTEMBER 1961

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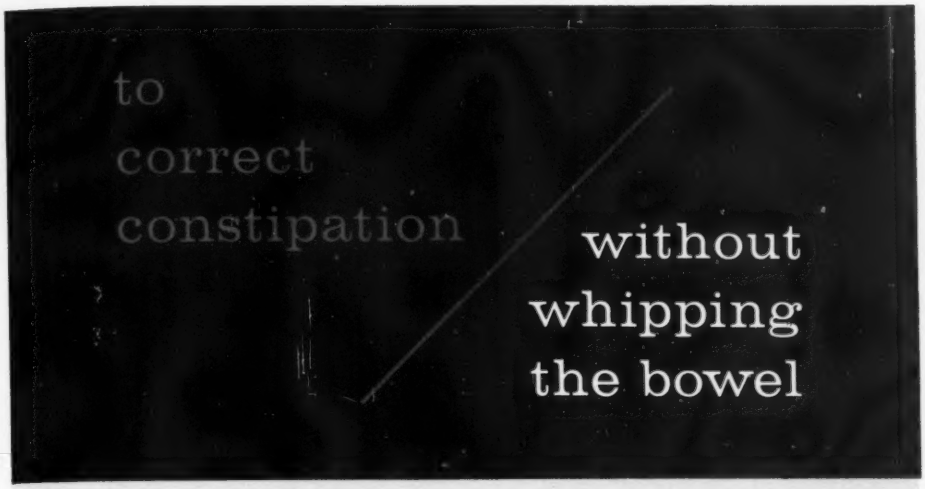

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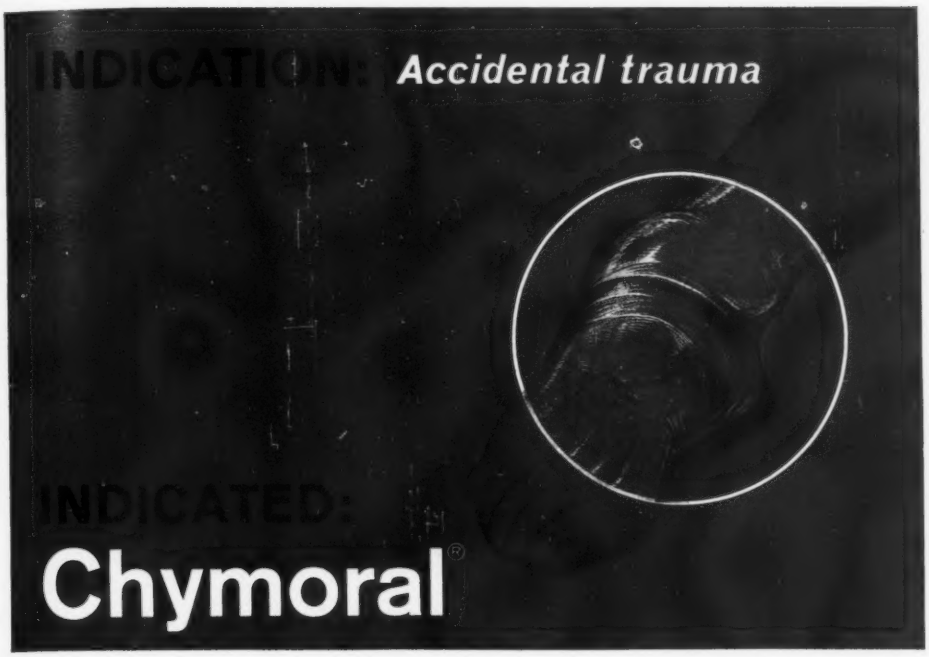

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1. Beck, C., *et al.*: Clin. Med. 7:519, 1960. 2. Teitel, L. H., *et al.*: Indust. Med. 29:150, 1960. 3. Billow, B. W., *et al.*: Southwestern Med. 41:286, 1960. 4. Clinical Reports to the Medical Department, Armour Pharmaceutical Company, 1960. 5. Taub, S. J.: Clin. Med. 7: 2575, 1960.

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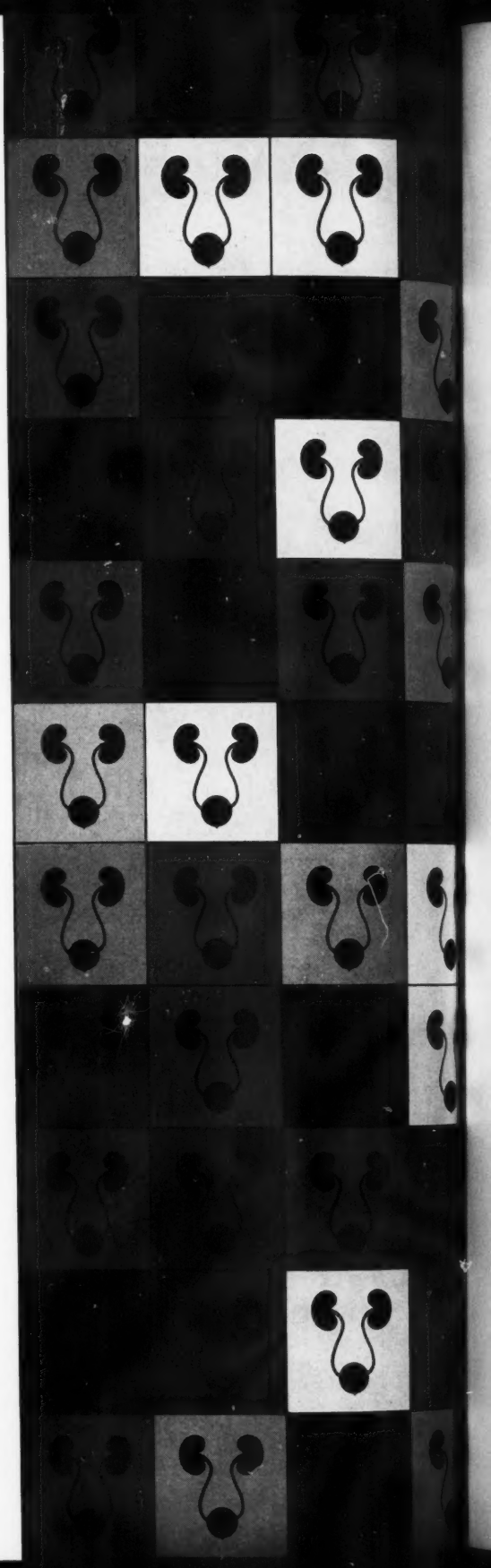

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References: 1. Bourque, J.-P., and Gauthier, G-E.: L'Union Medicale 89:640 (May) 1960. 2. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: Rocky Mountain M. J. 56:66 (Mar.) 1959. 3. Bourque, J.-P., and Joyal, J.: Canad. M.A.J. 68:337 (Apr.) 1953. 4. Hughes, J., Coppridge, W. M., and Roberts, L. C.: North Carolina M. J. 17:320 (July) 1956.

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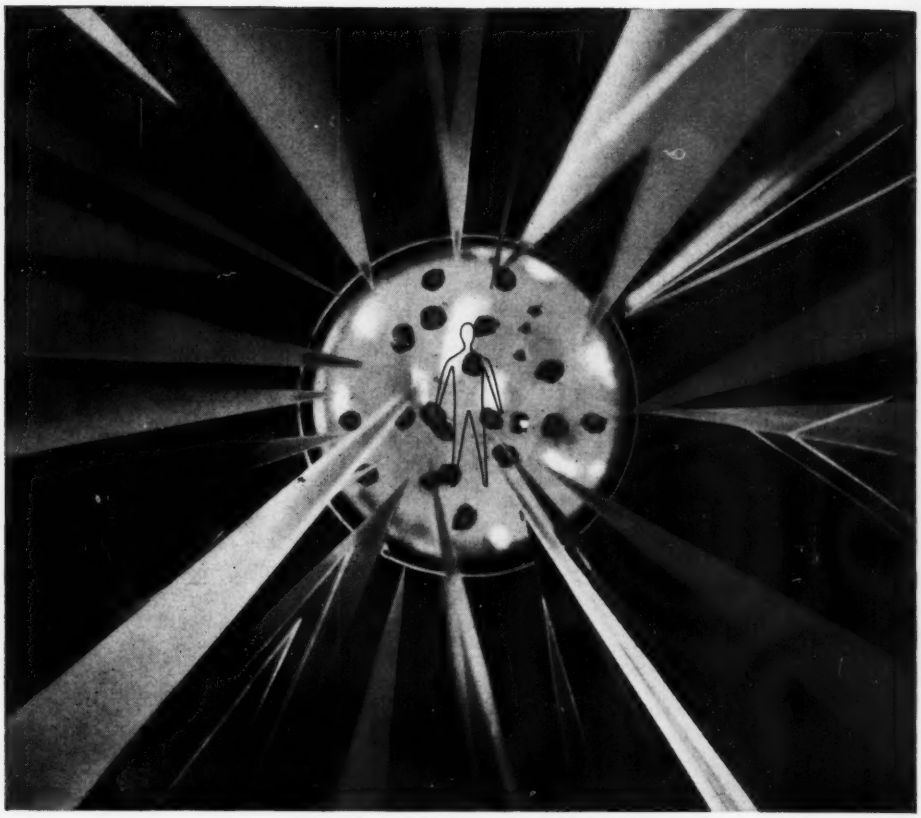

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Average Reductions In Systolic And Diastolic Blood Pressure Reported With Capla

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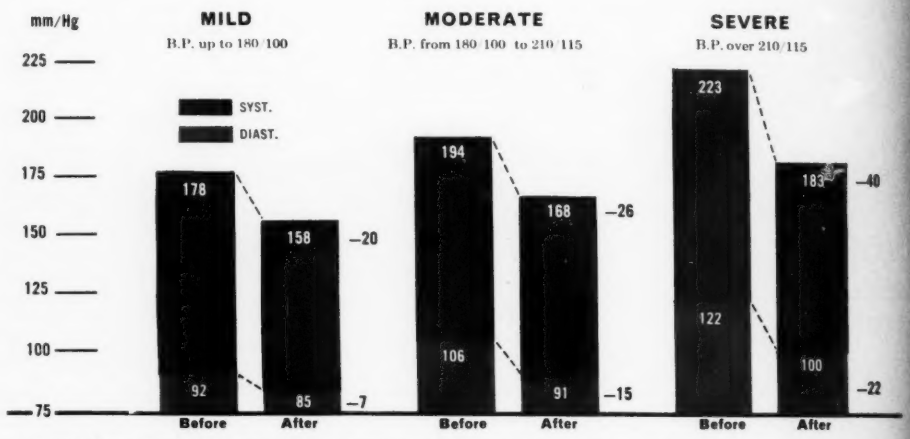

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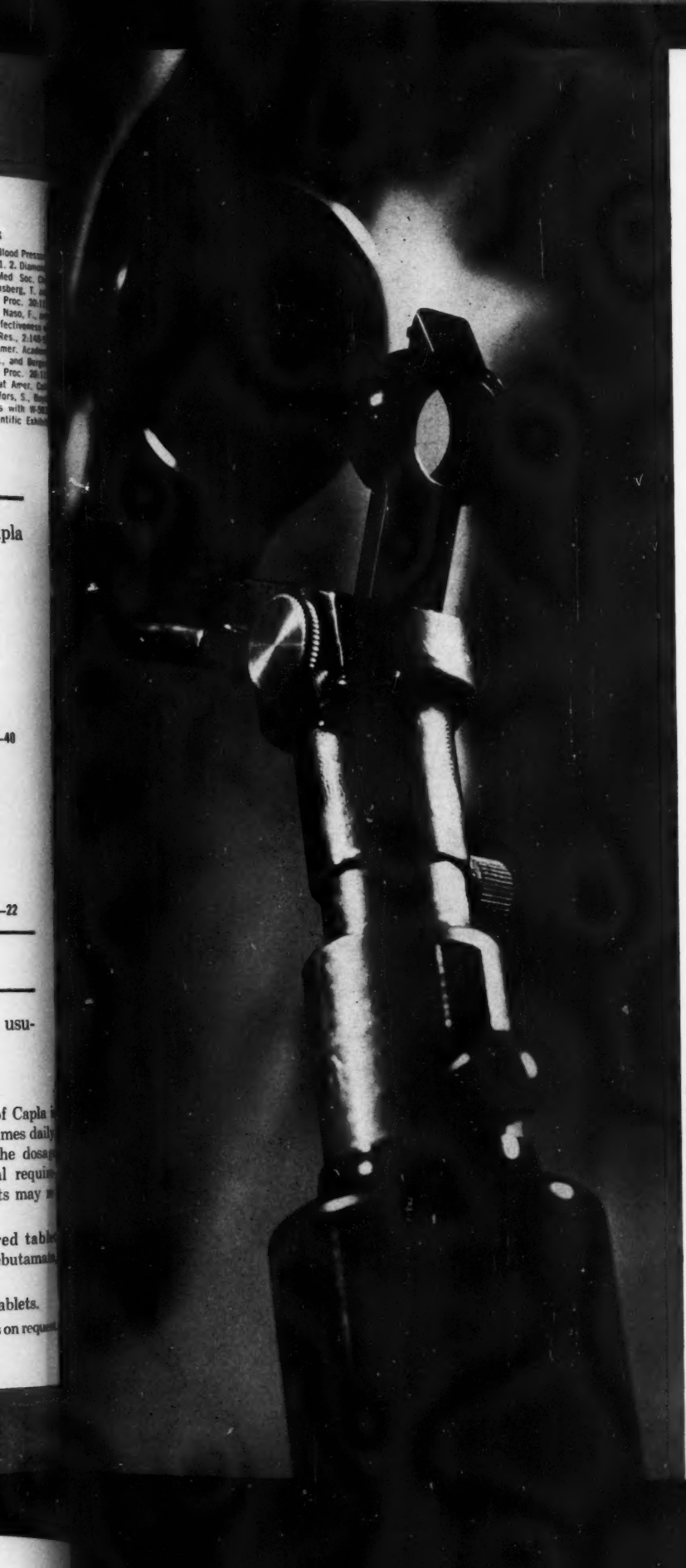
SUPPLIED: bottles of 100, scored tablets.

Literature and samples to physicians on request.



in bacterial otitis media

Panalba* promptly

to gain precious therapeutic hours

In the presence of bacterial infection, taking a culture to determine bacterial identity and sensitivity is desirable—but not always practical.

A rational clinical alternative is to launch therapy at once with Panalba, the antibiotic that provides the best odds for success.

Panalba is effective (in vitro) against 30 common pathogens, including the ubiquitous staph. Use of Panalba *from the outset* (even pending laboratory results) can gain precious hours of effective antibiotic treatment.

SUPPLIED: Capsules, each containing Panmycin* Phosphate (tetracycline phosphate complex), equivalent to 250 mg. tetracycline hydrochloride, and 125 mg. Albamycin,* as novobiocin sodium, in bottles of 16 and 100.

USUAL ADULT DOSAGE: 1 or 2 capsules 3 or 4 times a day.

SIDE EFFECTS: Panmycin Phosphate has a very low order of toxicity comparable to that of the other tetracyclines and is well tolerated clinically. Side reactions to therapeutic use are infrequent and consist principally of mild nausea and abdominal cramps.

Albamycin also has a relatively low order of toxicity. In a certain few patients, a yellow pigment has been found in the plasma. This pigment, apparently a metabolic by-product of the drug, is not necessarily associated with abnormal liver function tests or liver enlargement.

Urticaria and maculopapular dermatitis, a few cases of leukopenia and agranulocytosis have been reported in patients treated with Albamycin. These side effects usually disappear upon discontinuance of the drug.

CAUTION: Since the use of any antibiotic may result in overgrowth of nonsusceptible organisms, constant observation of the patient is essential. If new infections appear during therapy, appropriate measures should be taken. Total and differential blood counts should be made routinely during prolonged administration of Albamycin. The possibility of liver damage should be considered if a yellow pigment, a metabolic by-product of Albamycin, appears in the plasma. Panalba should be discontinued if allergic reactions that are not readily controlled by antihistaminic agents develop.

*Trademark, Reg. U. S. Pat. Off. June, 1961

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Panalba
your broad-spectrum antibiotic of first resort.

Upjohn

The Upjohn Company
Kalamazoo, Michigan

AN AMES CLINIQUICK®

CLINICAL BRIEFS FOR MODERN PRACTICE

Quality of diabetic control & Quantitation of urine-sugar

In the diagnosis of diabetes, the urine-sugar test may be little more than a screening adjuvant. But in the everyday management of diabetes, the urine-sugar test is the most practical guide we have.[1] Routine testing, however, should not only detect, but also determine the **quantity** of urine-sugar. Quantitative testing is essential for satisfactory adjustment of diet, exercise and medication. Furthermore, day-to-day control of diabetes is in the patient's hands. Quality of control is thus best assured by the urine-sugar test which permits the most accurate quantitation practicable **by the patient.**

CLINITEST® permits a high degree of practical accuracy and is very convenient.[2] Its clinically standardized sensitivity avoids trace reactions, and a standardized color chart minimizes error or indecision in reading results. CLINITEST distinguishes clearly the critical ¼%, ½%, ¾%, 1% and 2% urine-sugars. It is the only simple test that can show if the urine-sugar is over 2%.[3] Your nurse or technician will appreciate these advantages; your patient on oral hypoglycemic therapy will find them helpful. Furthermore, CLINITEST may be a vital adjunct in the management of the diabetic child or the adult with severe diabetes.

(1) Danowski, T. S.: Diabetes Mellitus, Baltimore, Williams & Wilkins, 1957, p. 239. (2) McCune, W. G.: M. Clin. North America 44:1479, 1960. (3) Ackerman, R. F., et al.: Diabetes 7:398, 1958.

FOR PRACTICAL ACCURACY OF URINE-SUGAR QUANTITATION

COLOR-CALIBRATED

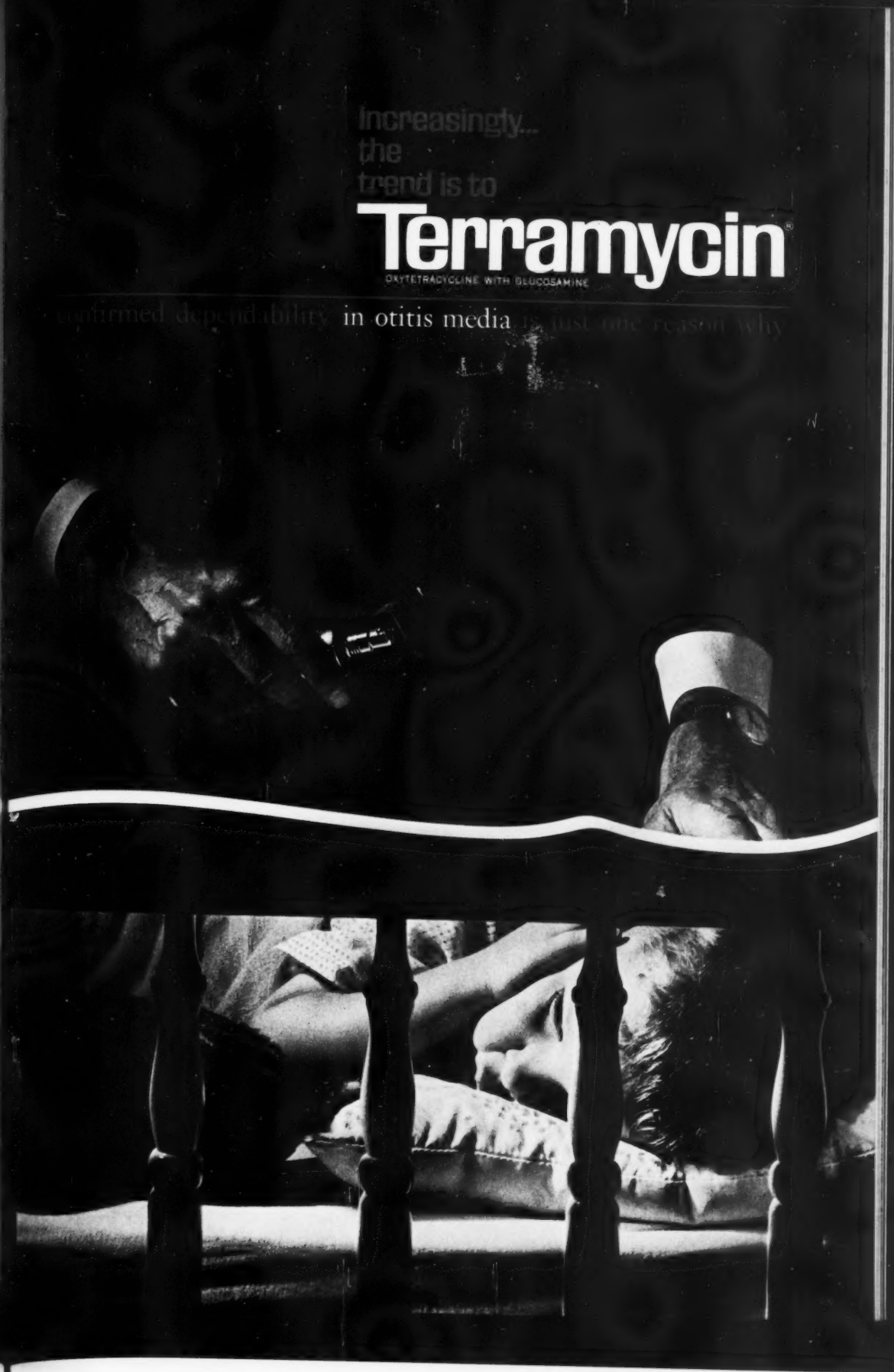
CLINITEST®

BRAND Reagent Tablets

Standardized urine-sugar test...with **GRAPHIC ANALYSIS RECORD**

A line connecting successive urine-sugar readings reveals at a glance how well diabetics are cooperating. Each CLINITEST Set and tablet refill contains this physician-patient aid. 01861

AMES COMPANY, INC. Elkhart, Indiana


Increasingly...
the
trend is to
Terramycin®
OXYTETRACYCLINE WITH GLUCOSAMINE
confirmed dependability in otitis media is just one reason why

*New evidence** demonstrates the effectiveness of Terramycin in *otitis media* . . . another reason for the trend to Terramycin.

In a series of 41 cases of otitis media, Terramycin not only "was often successful where other antibiotics had failed," but also showed that "it is extremely well tolerated"; oral dosage for infants was 250 to 375 mg. daily, for children, 500 mg. to 1 Gm. In many instances, oral therapy was preceded by intramuscular injection of Terramycin.

The authors concluded that "there is good reason to consider it [Terramycin] one of the most effective agents for treatment of infection of the upper respiratory tract."

These findings confirm the continuing vitality and broad-spectrum dependability of Terramycin, as reported through more than a decade of extensive clinical use.

In brief

The dependability of Terramycin in daily practice is based on its broad range of antimicrobial effectiveness, excellent toleration, and low order of toxicity. As with other broad-spectrum antibiotics, overgrowth of nonsusceptible organisms may develop. If this occurs, discontinue the medication and institute appropriate specific therapy as indicated by susceptibility testing. Glossitis and allergic reactions are rare. Aluminum hydroxide gel may decrease antibiotic absorption and is contraindicated.

More detailed professional information available on request.

another reason why the trend is to Terramycin—*versatility of dosage form:*

TERRAMYCIN Capsules—
250 mg. and 125 mg. per capsule—for convenient initial or maintenance therapy in adults and older children

TERRAMYCIN Intramuscular Solution—
50 mg./cc. in 10 cc. vials; 100 mg. and 250 mg. in 2 cc. ampules—preconstituted, ready to use where intramuscular therapy is indicated

Terramycin®

OXYTETRACYCLINE WITH GLUCOSAMINE

SYRUP PEDIATRIC DROPS

125 mg. per tsp. and 5 mg. per drop (100 mg./cc.), respectively

deliciously fruit-flavored aqueous dosage forms—conveniently preconstituted

Science for the world's well-being® Pfizer

PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc.
New York 17, N. Y.

*Jacques, A. A., and Fuchs, V. H.: J. Louisiana M. Soc. 113:200, May, 1961.

Pfizer *Science for the world's well-being®*

Dear Doctor:

Reports from our representatives indicate that many physicians would appreciate simplification for prescription-writing purposes of the names of Terramycin products in both the "plain" and the "Cosa" dosage forms.

The "Cosa" forms originated, you may recall, on the basis of clinical evidence of enhanced antibiotic absorption when glucosamine is employed in oral administration. To permit each physician individually to study this evidence and choose which form he would prefer to prescribe, we offered Terramycin in both forms—that is, in the regular Terramycin forms without glucosamine, and in the "Cosa" forms with glucosamine.

This distinction appears to be no longer necessary since glucosamine, a highly acceptable excipient for oral antibiotics, now is being incorporated uniformly in all such forms, thereby simplifying nomenclature and your prescription writing.

Accordingly, and effective immediately, forms incorporating glucosamine will be offered simply as Terramycin without the "Cosa" prefix.

To make clear just which forms are affected, please refer to the brief tabulation (below) of Terramycin dosage forms both *before* and *after* this change. We are also requesting our representative to call on you at an early date to answer any questions that may arise.

We feel certain that this action, prompted by your comments and those of many other physicians, will simplify your writing of prescriptions for Terramycin products.

We welcome your comments on this action and on any other phase of our operations, since it is our objective to render every service as efficiently as possible to our friends in the medical profession.

Sincerely,
PFIZER LABORATORIES

The following table indicates the former name and the current name of Terramycin systemic preparations:

FORMERLY NAMED	NOW NAMED
Cosa-Terramycin® Capsules	**Terramycin**® Capsules*
Cosa-Terrabon® Oral Suspension	**Terramycin** Syrup
Cosa-Terrabon Pediatric Drops	**Terramycin** Pediatric Drops

and simpler names for these Terramycin-containing formulations:

Cosa-Terrastatin® Capsules	**Terrastatin**® Capsules
Cosa-Terrastatin for Oral Suspension	**Terrastatin** for Oral Suspension
Cosa-Terracydin® Capsules	**Terracydin**® Capsules

. . . and these names remain unchanged:
Terramycin Intramuscular Solution
Terramycin Intravenous

**Terramycin Capsules* without glucosamine *are no longer available.*

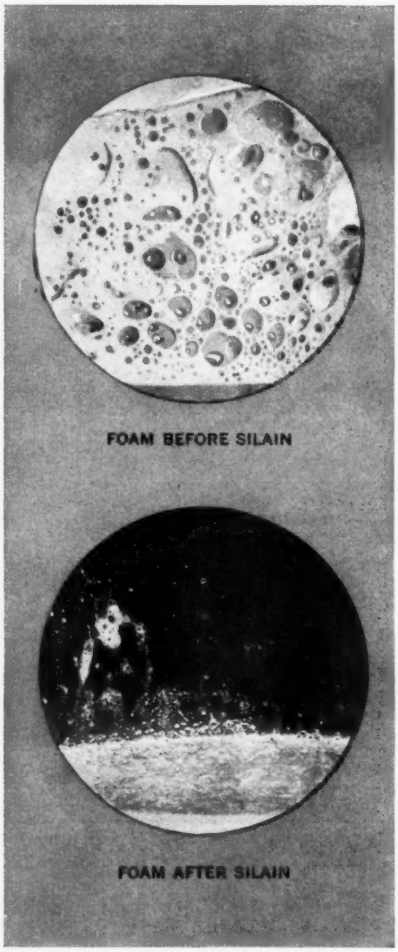
The clinical versatility of Terramycin is enhanced by its specialized dosage forms adapted to individual needs—*another reason for the trend to Terramycin.*

in abdominal distention

Associated with air swallowing, functional indigestion, spastic colitis, diverticulitis, peptic ulcer, postoperative gas.

NEW SILAIN™

The original brand of methylpolysiloxane



FOAM BEFORE SILAIN

FOAM AFTER SILAIN

a gastrointestinal DEFROTHICANT*

Air swallowing, abnormal peristalsis or "nervous indigestion" accelerates foaming. Foam and froth increase the volume of gastrointestinal contents causing discomfort.

SILAIN *dispels foam and froth*

Even normal peristalsis may produce thick, viscous foam in the presence of gastric mucin and gas forming digestive processes.

SILAIN *reduces increased volume*

By lowering interface cohesion, SILAIN breaks down the gas bubbles reducing the foam to a liquid.

SILAIN *provides fast relief*

Relief occurs promptly when foam is broken—entrapped gas is liberated for normal absorption or eliminated by belching or passing flatus—volume decreases immediately.

SILAIN *is safe*

A single non-toxic compound, SILAIN acts physically with no effect on gastrointestinal motility.

FORMULA: Each tablet contains 50 mg. methylpolysiloxane.

DOSAGE: 1 or 2 tablets after meals or more frequently if necessary.

AVAILABLE: 50 mg. tablets in bottles of 100.

Clinical trial supply on request

*DEFROTHICANT—The property of preventing and eliminating foam

U. S. Patent No. 2,951,011

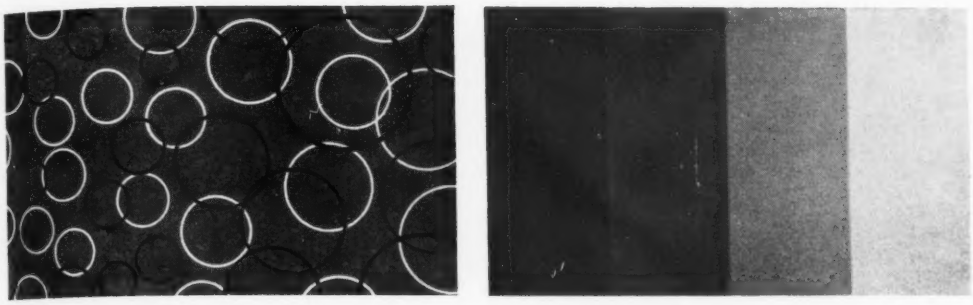
PLOUGH LABORATORIES, INC.

A Subsidiary of Plough, Inc., Memphis, Tennessee

in peptic ulcer, hyperacidity, heartburn

Control Gastric

GAS ACID



TABLETS

NEW SILAIN-GEL T.M.

DEFROTHICANT ANTACID

SILAIN-GEL *non-fatiguing, fruit-mint taste*

Releases Gas—The unique physical property of SILAIN breaks the frothy bubbles liberating the gas for elimination.

Neutralizes Acid—Specially balanced antacid formulation provides efficient neutralization.

DOSAGE—2 tablets after meals and at bedtime. The safety of Silain-Gel permits administration as often as necessary.

FORMULA—Each tablet contains: methylpolysiloxane 25 mg.; magnesium hydroxide 85 mg.; co-precipitated magnesium carbonate and aluminum hydroxide 282 mg.

REFERENCES

1. Roth, J.L.A. and Bockus, H.L.: Aerophagia—Med. Clin. N. Am. *41*:1673 (Nov.) 1957
2. Alvarez, W.C.: Gas in the Bowel: An Introduction to Gastroenterology; Paul B. Hoeber, Inc. Alvarez, W.C.; Syndrome of Reverse Peristalsis: Ibid
3. Barondes, R. de R. et al: The Silicones in Medicine. Mil. Surg. *106*:378, 1950
4. Cutting, W.: Toxicity of Silicones. Stanford M. Bull. *10*:23 (Feb.) 1952
5. Dailey, M. and Rider, J.: Silicone Antifoam Tablet in Gastroscopy. J.A.M.A. 155:859 (June) 1954
6. Rider, J.A. and Moeller, H.C.: Use of Silicone in the Treatment of Intestinal Gas and Bloating. J.A.M.A. *174*:2052 (Dec.) 1960
7. Rider, J.A.: Intestinal Gas and Bloating: Treatment with Methylpolysiloxane. Am. Pract. & Digest Treat. *11*:52 (Jan.) 1960

PLOUGH LABORATORIES, INC.

A Subsidiary of Plough, Inc., Memphis, Tennessee

me? use vinegar?

my doctor recommends Massengill Powder!

Patients like Massengill Powder. *Its clean, refreshing fragrance and convenience are acceptable to the most fastidious.*

Massengill Powder offers other sound advantages. Massengill Powder *is buffered to maintain a pH of 3 to 4.5 for 4 to 6 hours in ambulant patients . . . 24 hours in recumbent patients.* Vinegar douches are quickly neutralized.

Massengill Powder has a low surface tension (50 dynes/cm.; vinegar is 72 dynes/cm.). *This lower surface tension means more effective penetration and cleansing of the folds of the vaginal mucosa.*

Massengill Powder is a valuable adjunct in treatment of vaginal infections. Its low pH inhibits proliferation of fungal, protozoan and bacterial pathogens but is favorable to the beneficial Döderlein bacilli.

Patient cooperation is assured when Massengill Powder is recommended. Write for samples and literature.

Formula: Ammonium Alum, Boric Acid, Phenol, Eucalyptol, Berberine Salt, Menthol Isomers, Thymol and Methyl Salicylate.

MASSENGILL® POWDER

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco

Cremomycin® provides rapid relief of virtually all diarrheas

NEOMYCIN—actively bactericidal against a wide range of gram-negative intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

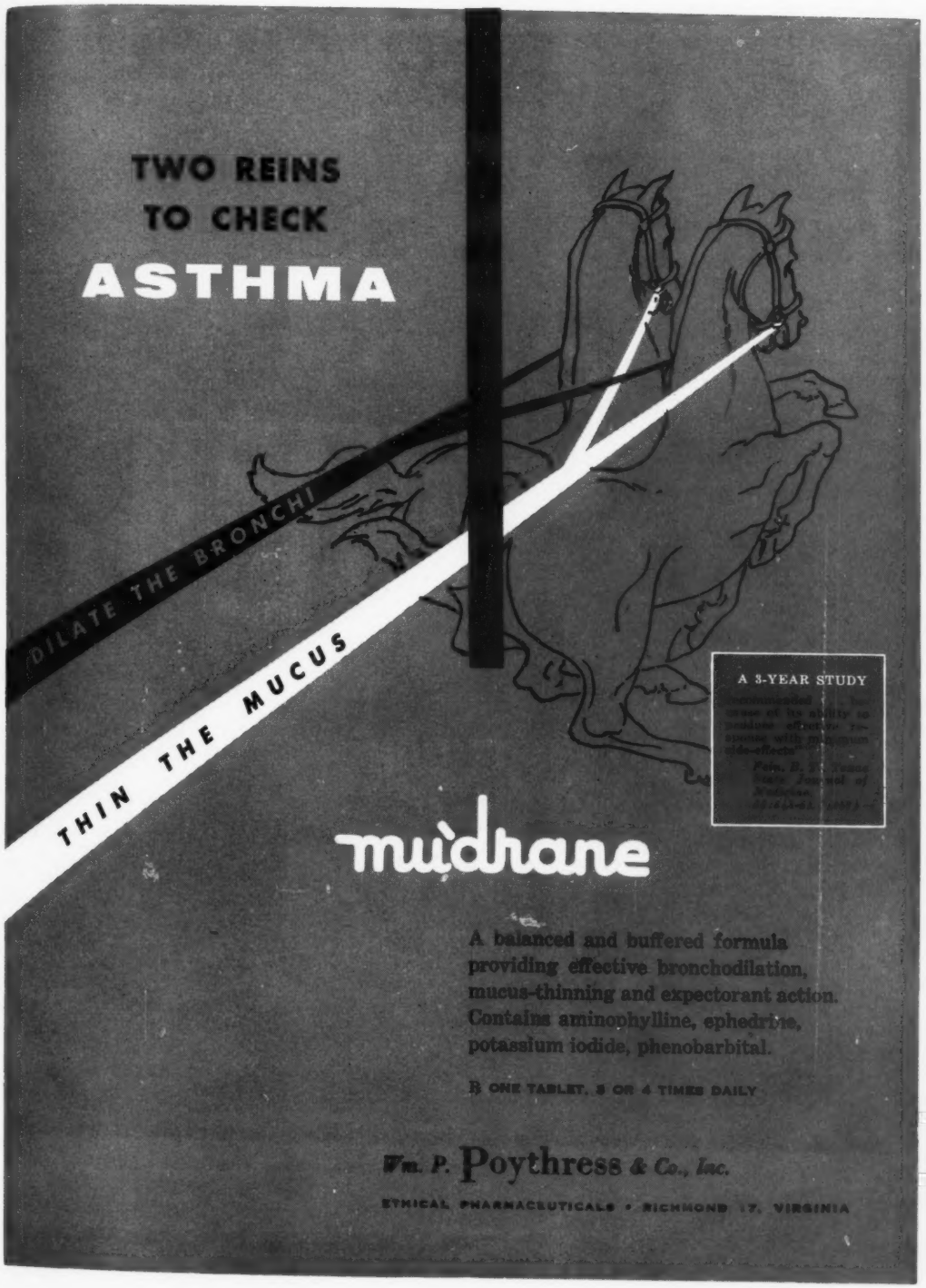
SULFASUXIDINE® succinylsulfathiazole—an ideal adjunct to neomycin because it is highly effective against Clostridia and certain other neomycin-resistant organisms.

KAOLIN AND PECTIN—coat and soothe the inflamed mucosa, adsorb toxins, help provide rapid symptomatic relief.

Additional information on CREMOMYCIN is available to physicians on request.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

CREMOMYCIN AND SULFASUXIDINE ARE TRADEMARKS OF MERCK & CO., INC.


TWO REINS
TO CHECK
ASTHMA
DILATE THE BRONCHI
THIN THE MUCUS
A 3-YEAR STUDY
mudrane
A balanced and buffered formula providing effective bronchodilation, mucus-thinning and expectorant action. Contains aminophylline, ephedrine, potassium iodide, phenobarbital.
1 ONE TABLET, 3 OR 4 TIMES DAILY
Wm. P. Poythress & Co., Inc.
ETHICAL PHARMACEUTICALS • RICHMOND 17, VIRGINIA

Lifts depression...as

You see an improvement within a few days
Thanks to your prompt treatment and the smooth action of Deprol, her depression is relieved and her anxiety and tension calmed – *often in a few days.* She eats well, sleeps well and soon returns to her normal activities.

...as it calms anxiety!

Smooth, balanced action lifts depression as it calms anxiety... rapidly and safely

Balances the mood – no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient – *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression.*

In contrast to such "seesaw" effects, Deprol's smooth, *balanced* action lifts depression as it calms anxiety – both at the same time.

Acts swiftly – the patient often feels better, sleeps better, within a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – often within a few days. Thus, the expense to the patient of long-term drug therapy can be avoided.

Acts safely – no danger of liver damage. Deprol does not produce liver damage, hypotension, psychotic reactions or changes in sexual function – frequently reported with other antidepressant drugs.

Bibliography *(13 clinical studies, 858 patients)*: **1.** Alexander, L. (35 patients): Chemotherapy of depression – Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. **2.** Bateman, J. C. and Carlton, H. N. (50 patients): Meprobamate and benactyzine hydrochloride (Deprol) as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy 6:648, Nov. 1959. **3.** Beerman, H. M. (44 patients): The treatment of depression with meprobamate and benactyzine hydrochloride. Western Med. 1:10, March 1960. **4.** Bell, J. L., Tauber, H., Santy, A. and Pulito, F. (77 patients): Treatment of depressive states in office practice. Dis. Nerv. System 20:263, June 1959. **5.** Breitner, C. (31 patients): On mental depressions. Dis. Nerv. System 20:142, (Section Two), May 1959. **6.** Gordon, P. E. (50 patients): Deprol in the treatment of depression. Dis. Nerv. System 21:215, April 1960. **7.** Landman, M. E. (50 patients): Clinical trial of a new antidepressive agent. J. M. Soc. New Jersey. In press, 1960. **8.** McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slattery, J. J., Konefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B. (128 patients): Treatment of depression – New technics and therapy. Am. Pract. & Digest Treat. 10:1525, Sept. 1959. **9.** Pennington, V. M. (135 patients): Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959. **10.** Rickels, K. and Ewing, J. H. (35 patients): Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959. **11.** Ruchwarger, A. (87 patients): Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959. **12.** Settel, E. (52 patients): Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Antibiotic Med. & Clin. Therapy 7:28, Jan. 1960. **13.** Splitter, S. R. (84 patients): Treatment of the anxious patient in general practice. J. Clin. & Exper. Psychopath. In press, April-June 1960.

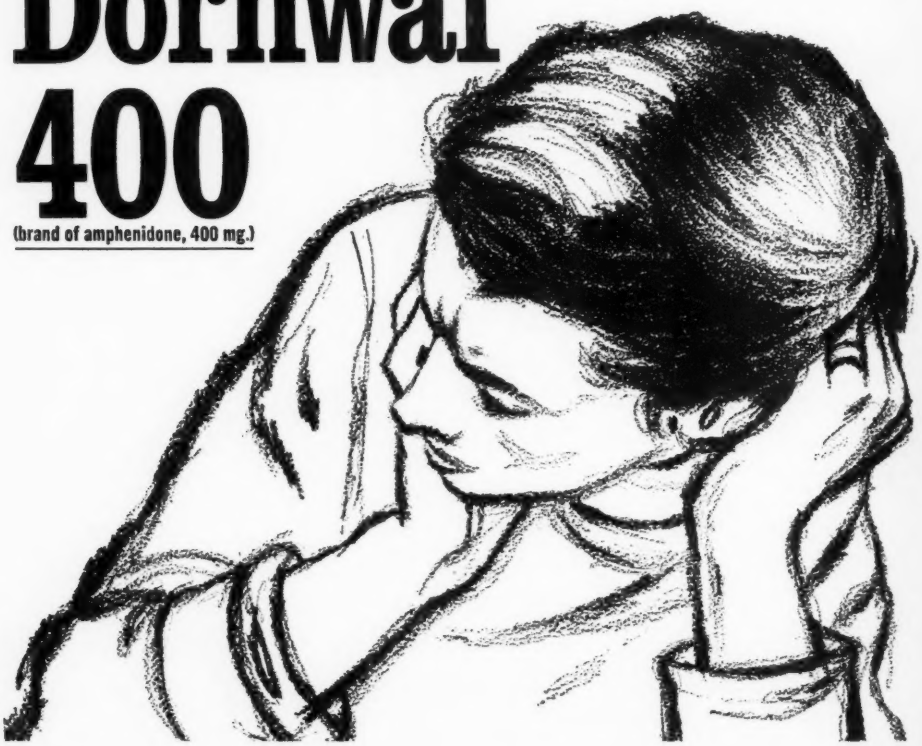
▲Deprol▲®

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate. **Supplied:** Bottles of 50 light-pink, scored tablets. **Write for literature and samples.**

WALLACE LABORATORIES / *Cranbury, N. J.*

AVAILABLE NOW
INCREASED POTENCY
GREATER ECONOMY
with
Dornwal®
400
(brand of amphenidone, 400 mg.)



impressively effective against tension headache*

Dornwal 400 relaxes the musculature of the head and neck involved in tension headache and by doing so breaks the vicious cycle between psychological tension and muscular tension. Dornwal 400 also relieves anxiety and tension states quickly and effectively, usually without sedation or drowsiness. It is particularly suited to the active patient because it is relatively free from side effects such as depression and depersonalization. Some patients are relieved of their symptoms in as little as half an hour.

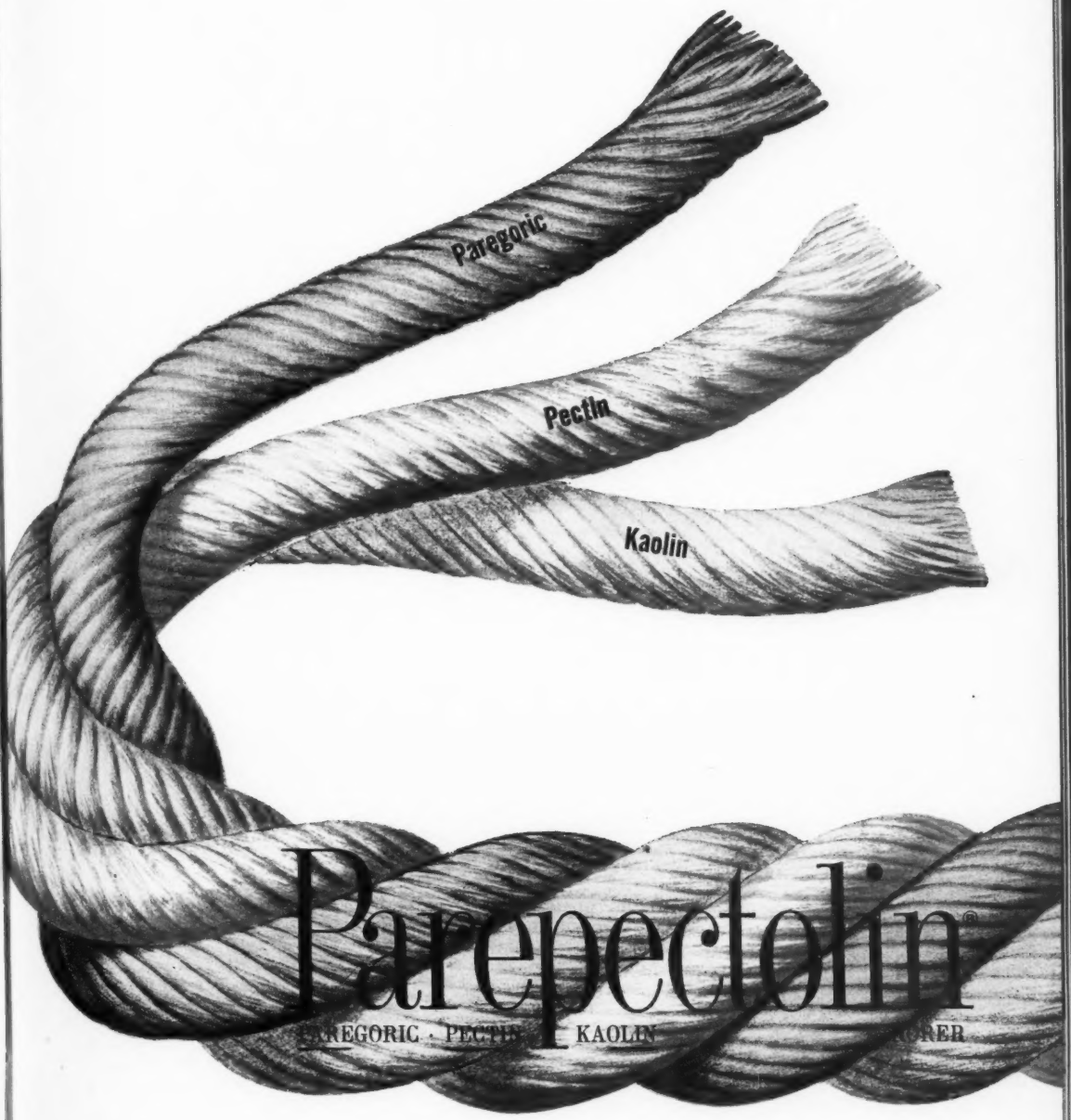
Dornwal 200 (amphenidone, 200 mg.), for similar conditions where lower dosage levels are adequate. Dornwal 100 (amphenidone, 100 mg.) is effective in the treatment of emotionally disturbed children.

Supplied: Dornwal 400—400 mg. green scored tablets. Dornwal 200—200 mg. yellow scored tablets. Dornwal 100 (Pediatric)—100 mg. pink tablets. Bottles of 100 and 500.

Maltbie Laboratories Division
Wallace & Tiernan Inc., Belleville 9, N. J.

*Dixon, H. H.; Dickel, H. A., and Dixon, H. H., Jr.: "Clinical and Electromyographic Appraisal of Aminophenylpyridone," Northwest Med. 60:277 (March) 1961.

CONTROL DIARRHEA... the traditional and time-tested triad of effective and safe agents



Pleasant taste *plus* predictable, prompt response in diarrhea

Parepectolin combines paregoric, pectin, kaolin in *a balanced, stable colloidal suspension,* with a smooth, creamy consistency and a pleasant, mildly aromatic flavor. Parepectolin is compatible with antibiotics, and retains its uniform consistency and its good flavor.

Parepectolin; each fluid ounce—Paregoric (equivalent) 1.0 dram, Pectin 2.5 gr., Kaolin (specially purified) 85 gr. Bottles of 4 and 8 fluid ounces.

ROER — WILLIAM H. RORER, INC. PHILADELPHIA, PENNSYLVANIA

from mental confusion to the right frame of mind

continuous, 24-hour cerebral oxygenation for the aging patient. By stimulating respiratory and circulatory function, GERONIAZOL TT* relieves mental confusion, depression, anxiety, and emotional instability—frequent problems in patients after forty—due to presenile changes in the vasculature of the brain. Notable benefit usually is seen within one to three weeks of therapy. It improves appetite, sleep pattern, and outlook—and GERONIAZOL TT* is non-hypertensive, non-excitatory.

Neither a tranquilizer nor a psychic energizer, GERONIAZOL TT* provides a physiologic stimulation of the cerebrum to permit the patient to adjust to his surroundings, become part of life itself again—and *attain the right frame of mind.*

References: 1. Curran, T. R., and Phelps, D. K.: Am. Pract. & Dig. Treat. *11:* 617, 1960. 2. Levy, S.: J.A.M.A. *153:* 1260, 1953. 3. Connolly, R.: W. Va. Med. J. *56:* 263, 1960.

Each TEMPOTROL contains: Pentylenetetrazol, 300 mg.; [illegible] Nicotinic Acid, 150 mg.

Indications: Respiratory and circulatory stimulant for the aged [illegible] debilitated with symptoms of [illegible] confusion, depression, anxiety [illegible] arteriosclerotic psychosis.

Contraindications: None known [illegible] recommended dosage.

Dosage: One GERONIAZOL TT* tablet, b. i. d.

Supplied: Bottles of 42 tablets ([illegible] weeks' treatment).

GERONIAZOL® TT*

*TEMPOTROL® (Time Controlled Therapy)

PHILIPS ROXANE, INC. Columbus 16, Ohio

WHY GANTRISIN IS PREFERRED

High urine levels are not enough: for successful eradication of urinary pathogens, the anti-infective agent must reach effective concentrations in blood and tissues, as well as in the urine. Gantrisin does this. Unlike compounds that inhibit bacterial growth in the urine and on epithelial surfaces only, Gantrisin acts in deeper tissue layers, too. Effective against common urinary pathogens (including many resistant strains) and highly soluble at full pH range, Gantrisin may be prescribed with unhesitating confidence in acute and chronic infections and for routine prophylaxis. Reports in hundreds of journals and scores of textbooks reflect the position of Gantrisin as a drug of choice in genitourinary infections.

Consult literature and dosage information, available on request, before prescribing.

IN GENITOURINARY INFECTIONS

Gantrisin

THE QUALITY OF GREATNESS

FOR PROVEN EFFICACY IN INFECTIOUS DIARRHEAS

Humatin® KAPSEALS

(paromomycin, Parke-Davis)

A WELL-TOLERATED ANTIBIOTIC-AMEBICIDE

HUMATIN possesses high antibacterial and antiamebic activities, coupled with a low order of oral toxicity.[1] Because it is effective against many gram-negative pathogens, HUMATIN has proved valuable in the treatment of infectious diarrheas and other enteric infections, most of which are caused by bacilli of the gram-negative group.[2-5] Characteristic of the favorable response to HUMATIN is a prompt reduction in the number of stools per day, a decrease in fever, and rapid alleviation of other symptoms of infection.[2,3,5] HUMATIN is also useful in all phases of intestinal amebiasis,[1,5-12] and has shown promise of being useful in the preoperative suppression of intestinal flora,[5] and in the adjunctive management of hepatic coma.[13-15]

HUMATIN is not appreciably absorbed from the gastrointestinal tract and is, therefore, not effective against systemic infections. Systemic toxicity has not been a problem. *See medical brochure for details of administration, precautions, and dosage.*

SUPPLIED: HUMATIN (paromomycin, Parke-Davis) is available as the sulfate in Kapseals,® each containing the equivalent of 250 mg. of base, in bottles of 16.

REFERENCES: (1) Coffey, G. L., *et al.: Antibiotics & Chemother.* 9:730, 1959. (2) Courtney, K. O.; Thompson, P. E.; Hodgkinson, R., & Fitzsimmons, J. R.: *Antibiotics Annual* 7:304, 1959-1960. (3) Godenne, G. D.: *ibid.*, 310. (4) McMath, W. F. T., & Hussain, K. K.: *Pub. Health* 73:328, 1959. (5) Personal Communications to Department of Clinical Investigation, Parke, Davis & Company, 1959. (6) Shafei, A. Z.: *Antibiotic Med. & Clin. Therapy* 6:275, 1959. (7) Lopez Elias, F., & Oliver-Gonzalez, J.: *Antibiotic Med. & Clin. Therapy* 6:584, 1959. (8) Carter, C. H.: *Antibiotic Med. & Clin. Therapy* 6:586, 1959. (9) Thompson, P. E., *et al.: Antibiotics & Chemother.* 9:618, 1959. (10) Dooner, H. P.: *Antibiotic Med. & Clin. Therapy* 7:486, 1960. (11) Coles, H. M. T., *et al.: Lancet* 1:944, 1960. (12) Moffett, H. F., & Toh, S. H.: *Antibiotic Med. & Clin. Therapy* 7:569, 1960. (13) Fast, B. B.; Wolfe, S. J.; Stormont, J. M., & Davidson, C. S.: *Arch. Int. Med.* 101:467, 1958. (14) Mackie, J. E.; Stormont, J. M.; Hollister, R. M., & Davidson, C. S.: *New England J. Med.* 259:1151, 1958. (15) Stormont, J. M.; Mackie, J. E., & Davidson, C. S.: *New England J. Med.* 259:1145, 1958.

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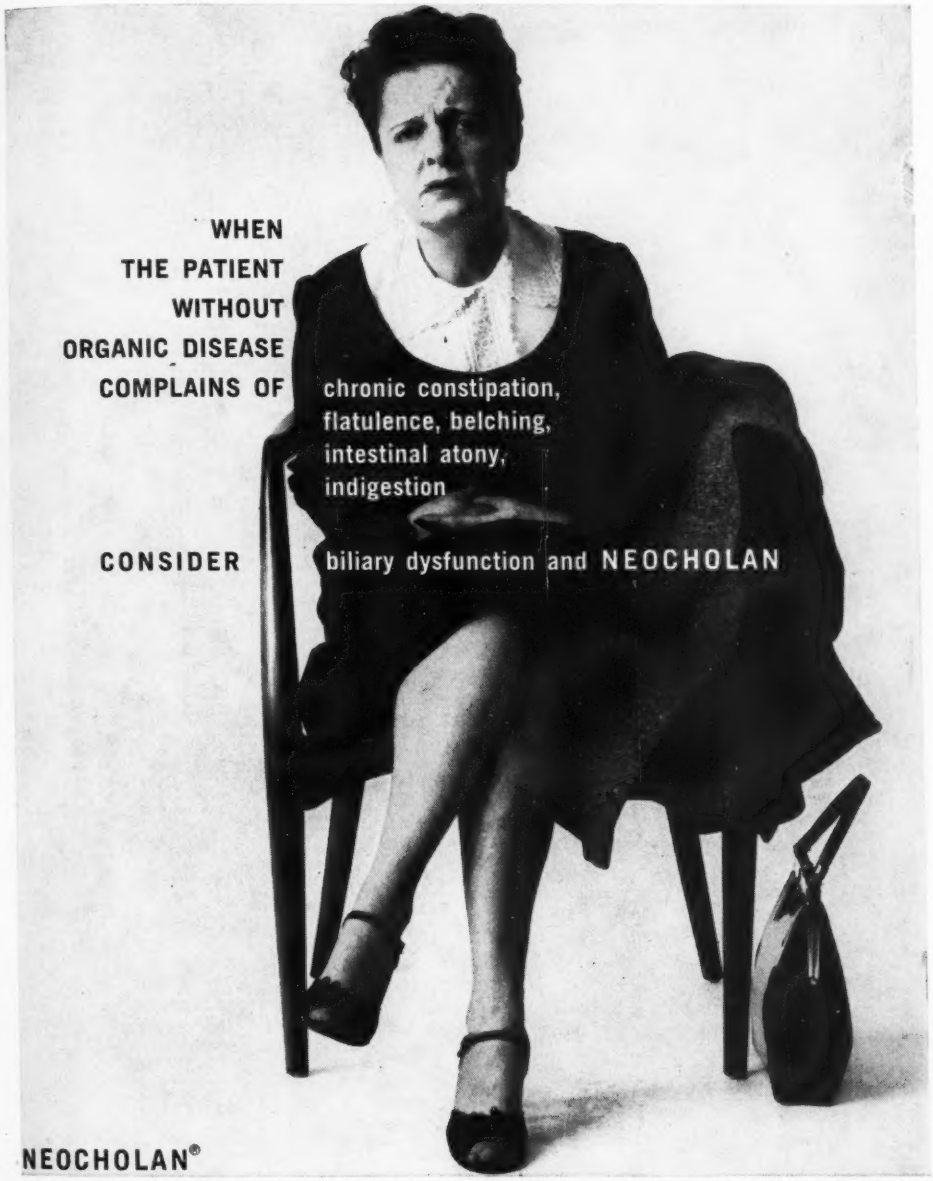
PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan



NEOCHOLAN®

Your patient will often respond promptly to Neocholan therapy. It greatly increases the flow of thin, nonviscid bile and corrects biliary stasis by flushing the biliary system. It also relaxes intestinal spasm, resulting in an unimpeded flow of bile and pancreatic juice into the small intestine. Neocholan helps to promote proper digestion and absorption of nutrients. It also encourages normal peristalsis by restoring intestinal tone.

Each tablet provides: Dehydrocholic Acid Compound, P-M Co. 265 mg. (Dehydrocholic Acid, 250 mg.); Homatropine methylbromide 1.2 mg.; Phenobarbital 8.0 mg. Supplied in bottles of 100 tablets.

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(oxyphencyclimine plus ATARAX®)

In peptic ulcer and functional bowel distress
ENARAX provides dual relief of symptoms: it decreases acid flow and spasm . . . **and** relieves tension.

Plus protection against flare-ups
ENARAX works continuously . . . gives dependable 24-hour control, usually with b.i.d. dosage.

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Dosage: The usual dosage is one ENARAX 5 or ENARAX 10 tablet twice daily—preferably in the morning and before retiring. Maintenance dose should be adjusted according to therapeutic response. Use with caution in patients with prostatic hypertrophy and only with ophthalmological supervision in glaucoma.

Supplied: ENARAX 5 (oxyphencyclimine HCl 5 mg., Atarax 25 mg.) and ENARAX 10 (oxyphencyclimine HCl 10 mg., Atarax 25 mg.), bottles of 60.

1. Hock, C. W.: Am. J. Gastroenterol. **34**:293 (Sept.) 1960.
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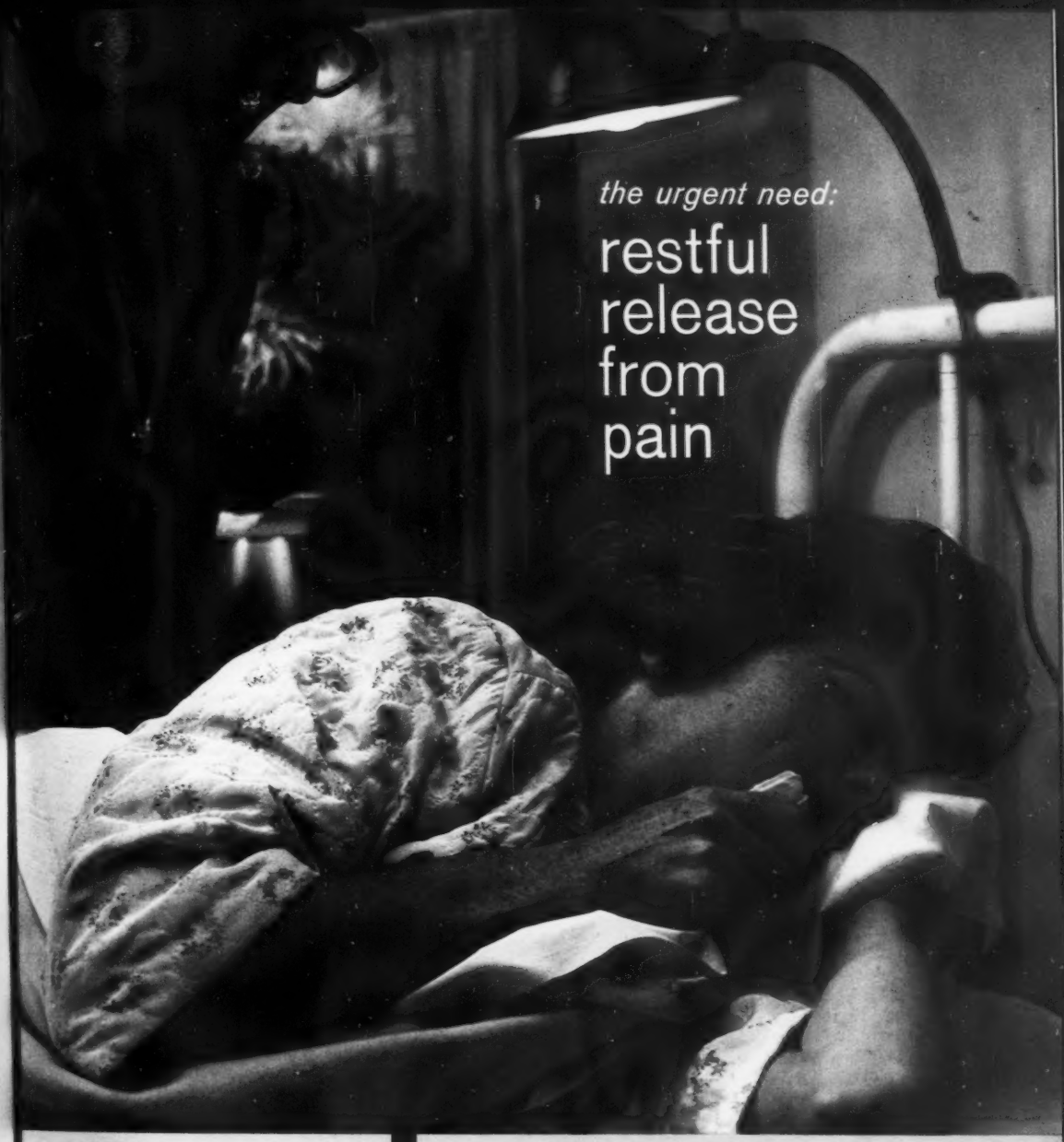
Science for the World's Well-Being®



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PHENAPHEN with Codeine ..... ¼ gr.

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SUPPLY: Bottles of 100 and 500 capsules.

sedative-enhanced analgesia

To each "according to his need" — maximum safe analgesia through time-and-pain-tested synergistic formulations, in four strengths for individualized prescription.

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¼ gr., ½ gr., 1 gr.

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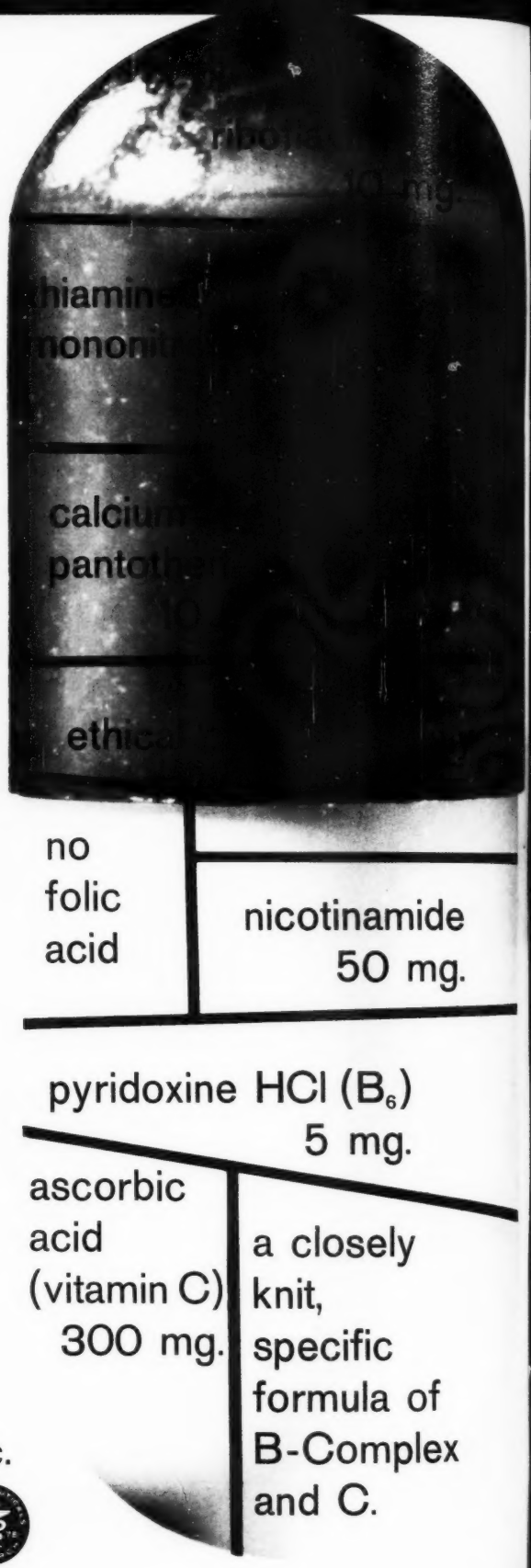

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In virtually all forms of arthritic disorder, Butazolidin affords prompt symptomatic and objective improvement without development of tolerance... without danger of hypercortisonism.

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Clinically Proven Results...controls infection/reduces exudation/stops pruritus/relieves pain/does not distort otic landmarks/physiologic pH/virtually nonsensitizing and nonirritating. FORMULA: Neomycin (from sulfate), 3.5 mg., and sodium propionate, 50 mg. per cc. Available in 15 cc. dropper bottles.

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Effective relief in 82% of 3334 cases.* Sterile Otic Drops—ideal for use when inflammation is present. Provides the same outstanding clinical benefits of Otobiotic, plus prednisolone for anti-inflammatory effectiveness. FORMULA: Prednisolone acetate, 5 mg., neomycin (from sulfate), 3.5 mg. and sodium propionate, 50 mg. per cc. Available in 5 cc. bottles with "steri-sealed" dropper.
*Case reports on file, White Laboratories.

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YOUR ALLERGIC PATIENT REMAINS ASYMPTOMATIC AND ALERT!

Pulvules® (Sustained-Action Tablets) 4 mg. and 8 mg., bottles of 100. TABLETS: 2 mg. scored, bottles of 100. SYRUP: 2mg./tsp., pint bottles.

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In nasal congestion and rhinorrhea due to head colds, allergies and sinusitis—
Decongests Nasal and Sinus Passages
Dries Mucous Secretions!
A sensibly simple formula: Disomer (dexbrompheniramine maleate), 2 mg., pseudoephedrine sulfate, 60 mg. Available in bottles of 100 scored tablets.

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In response to
innumerable requests
from dermatologists

***Winthrop Laboratories
now makes available***

TRIQUIN®

FOR LUPUS ERYTHEMATOSUS AND LIGHT-SENSITIVITY ERUPTIONS

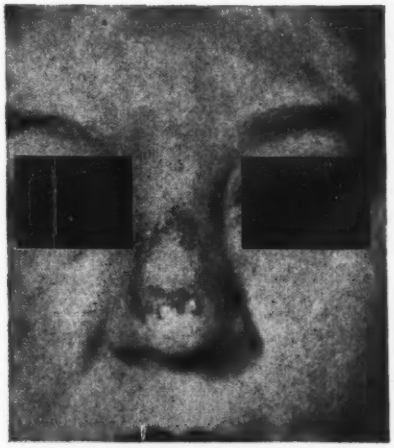
WHAT IT IS:
A combination of Atabrine® hydrochloride 25 mg., Aralen® phosphate 65 mg. and Plaquenil® sulfate 50 mg.

WHAT IT'S FOR:
Treatment of lupus erythematosus (chronic discoid type) and polymorphic light eruptions (light-sensitivity eruptions, solar urticaria or dermatitis).

HOW IT ACTS:
Each of the three components produces beneficial response in lupus erythematosus and light-sensitivity eruptions. Since the dose of each of the Triquin components is very low, overall toxicity is reduced and clinical tolerance improved. Furthermore, the three components appear to act synergistically.

HOW SUPPLIED:
Triquin tablets in bottles of 100, sold on prescription only.

Write for TRIQUIN booklet.



DOSAGE:
Lupus. Average initial adult dose, 1 or 2 tablets after meals and at bedtime. Dosage should be reduced gradually at two week intervals to 1 or 2 daily.

Light-Sensitivity Eruptions. Average initial adult dose, 1 tablet after breakfast and lunch. May be reduced after several weeks to maintenance dosage of 1 tablet daily.

Triquin, Atabrine (brand of quinacrine), Aralen (brand of chloroquine), and Plaquenil (brand of hydroxychloroquine), trademarks reg. U.S. Pat. Off.

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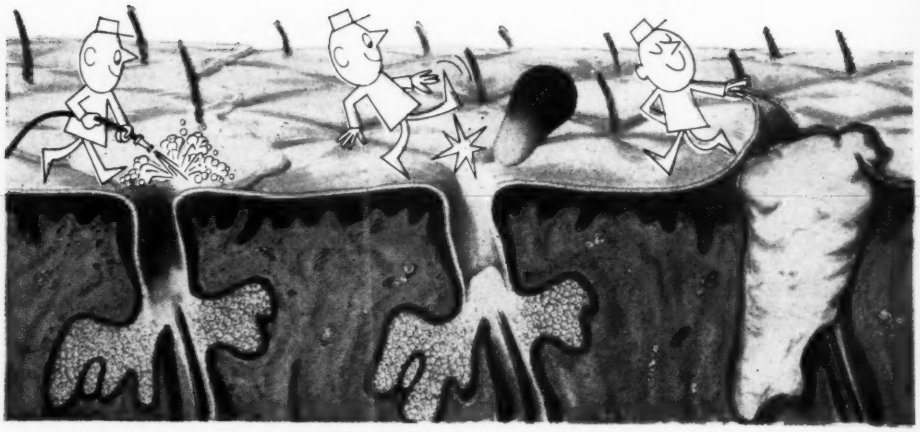

Fostex® treats pimples·blackheads·acne while they wash

degreases the skin
helps remove blackheads
dries and peels the skin

Patients like Fostex because it's so easy to use. Instead of using soap, they simply wash acne skin with Fostex Cream or Fostex Cake 2 to 4 times daily.

Fostex contains: Sebulytic® base (unique, penetrating, surface-active combination of soapless cleansers and wetting agents*) with remarkable antiseborrheic, keratolytic and antibacterial actions . . . enhanced by micro-pulverized sulfur 2%, salicylic acid 2% and hexachlorophene 1%.

*sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate and sodium dioctyl sulfosuccinate.

Fostex Cream and Fostex Cake are interchangeable for therapeutic washing of the skin. Fostex Cream is approximately twice as drying as Fostex Cake. Supplied: Fostex Cake—bar form. Fostex Cream—4.5 oz. jars. Also used as a therapeutic shampoo in dandruff and oily scalp.

And . . . since continuous 24-hour drying and peeling of acne skin is essential, FOSTRIL (a new, flesh-tinted drying lotion) should be used once or twice daily in addition to Fostex therapeutic washings. Fostril® contains Liposec® (polyoxyethylene lauryl ether), a new, surface-active drying agent used for the first time in acne treatment. This agent, with 2% micropulverized sulfur and a zinc oxide, talc and bentonite base, provides Fostril with excellent drying properties. Fostril also contains 1% hexachlorophene.

Available: Fostril, 1½ oz. tubes. Fostril-HC (¼% hydrocortisone) 25 gm. tubes.

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CHYMOLASE

CHYMOTRYPSIN, W-T

IN AQUEOUS GELATIN SOLUTION

for reduction of local inflammation, edema, congestion...

INDICATIONS

CIRCULATORY DISORDERS
Phlebothrombosis and thrombophlebitis.

ACCIDENTAL INJURIES
Sprains, strains, bruises, hematomas.

BRONCHOPULMONARY DISORDERS
Bronchiectasis, bronchial asthma, emphysema.

ACUTE INFLAMMATION
Bursitis, arthritis and cellulitis.

TISSUE NECROSIS
Varicose, diabetic and decubitus ulcers.

SURGERY
Inflammation, edema and hematoma.

OBSTETRICS
Episiotomies, phlebitis, postphlebitic edema, postpartum breast engorgement.

Dosage: 0.5 cc to 1.0 cc deeply in the gluteal muscle once or twice daily as indicated.

Supplied: In 1 cc ampuls and 5 cc vials, each cc containing 5000 units of proteolytic activity in an aqueous solution containing 50 mg gelatin, 0.1 mg propyl parahydroxybenzoate, 0.9 mg methyl parahydroxybenzoate.

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Effective

TRIPLE SULFA THERAPY is safe at levels of pH 5.5 or lower where the possibility of crystalluria would be greatest.

TRI-AZO-MUL
TRI-AZO-TAB

TRI-AZO-MUL

Each 100 cc contains:

Sulfadiazine (Microcrystalline)	3.381 gm.
Sulfamerazine (Microcrystalline)	3.381 gm.
Sulfamethazine (Microcrystalline)	3.381 gm.

In a palatable, stable emulsion pleasantly flavored with True Raspberry Flavor. Each average teaspoonful (80 min.) represents .5 gm. (7.7 grs.) of three combined sulfa drugs in suspension. Supplied in pint bottles only.

CONTRAINDICATIONS: Sulfonamides are potent drugs, and may cause toxic reactions. Sulfonamides, therefore, should be given only under constant supervision of a Physician.

TRI-AZO-TAB

Each tablet represents:

Sulfadiazine	0.166 gm. (2.57 gr.)
Sulfamerazine	0.166 gm. (2.57 gr.)
Sulfamethazine	0.166 gm. (2.57 gr.)

Available in White or Pink colored tablets in bottles of 100, 500 or 1,000.

TRI-AZO-MUL (citrated) offers the same formula as TRI-AZO-MUL (plain) with sodium citrate (17.5 gm.).

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Another Established Need Product . . . .

Serving the physician's needs since 1901

in acute, uncomplicated urinary tract infections... effective low dose therapy with

FURADANTIN® 50 mg. q.i.d.

brand of nitrofurantoin

In acute infections of the urinary tract involving gram-negative organisms (predominantly coli-aerogenes group), Welling and colleagues[1] found that patients responded clinically to FURADANTIN 50 mg. q.i.d. "as readily as to 100 mg. dosage." Particularly with moderate fluid restriction, Thompson and Amar[2] consider that 50 mg. FURADANTIN tablets provide "urine concentrations sufficient to clear the majority of acute uncomplicated infections"—and with "complete obviation of nausea." Lippman et al.[3] also reported minimal side effects with FURADANTIN 50 mg. q.i.d. in prolonged prophylactic use.

Patients who do not respond to FURADANTIN 50 mg. q.i.d. after 2 or 3 days should be given an increased dosage—FURADANTIN 100 mg. q.i.d. Patients with complicated, chronic or refractory urinary tract infections should receive FURADANTIN 100 mg. q.i.d. from the outset. FURADANTIN is available in *Tablets* of 50 mg. and 100 mg., and in an *Oral Suspension* containing 25 mg. of FURADANTIN per 5 cc. teaspoonful.

REFERENCES: 1. Welling, A.; Watkins, W.W., and Raines, S.L.: J. Urol. *77*:773, 1957. 2. Thompson, I.A., and Amar, A.D.: J. Urol. *82*:387, 1959. 3. Lippman, R.W.; Wrobel, C.J.; Rees, R., and Hoyt, R.: J. Urol. *80*:77, 1958.

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uterine relaxation
with no side effects

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THREATENED AND HABITUAL ABORTION
AND DYSMENORRHEA

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LUTREXIN has been used successfully for the past eight years in thousands of cases of dysmenorrhea, premature labor and threatened and habitual abortion.

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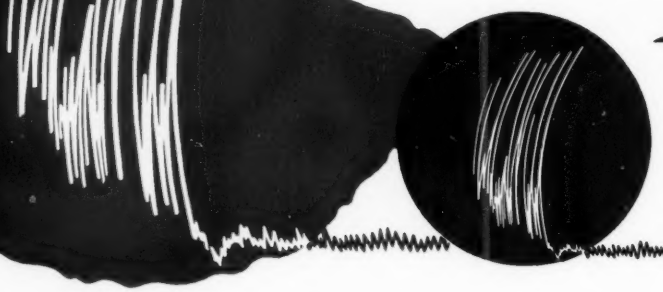
Being a non-steroid, LUTREXIN causes no untoward by-effects even when massive doses are used.

Supplied In Bottles Of 25 — 3000 Unit Tablets

1. *Bryant, H. H.: to be published.*
2. *Krantz, J. C.; Bryant, H. H. and Carr, C. J.; Surg., Gyn. & Obst., 90: 372-375, 1950.*



in vivo measurement
of LUTREXIN on
contracting uterine muscle

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Southern Medical Journal

PUBLISHED BY SOUTHERN MEDICAL ASSOCIATION

September 1961

Vulnerability to Stroke Secondary to Occlusion of the Internal Carotid Artery: Its Evaluation by Angiography*

HOMER D. KIRGIS, M.D., RAEBURN C. LLEWELLYN, M.D., and EDWARD McC. PEEBLES, Ph.D.,† *New Orleans, La.*

Congenital anomalies in the distribution of the branches of the internal carotid artery are varied. Such anomalies are of great importance in the vulnerability of the brain to stroke upon the development of atheromatous plaques. Angiography may demonstrate these variations from the normal.

SURGICAL OCCLUSION of the common carotid or internal carotid artery is performed comparatively often, as in the treatment of ruptured intracranial aneurysms and neoplasms of the head and neck. Review of the literature reveals wide divergence of opinions concerning the anticipated tolerance to obstruction of either of these arteries. In general, however, the earlier reports suggest that sacrificing the direct carotid flow by ligation of either the common or internal carotid artery is potentially more dangerous than is currently believed to be the case.[1,2] Undoubtedly, improvement in surgical technics and in general supportive measures has contributed largely to this reversal of opinion.

Recently, the converse of sacrificing the carotid blood flow on one side has become an even more common clinical consideration. This has resulted from the demonstration that both major and minor strokes are often primarily the result of partial or complete occlusion of the carotid system supplying the affected hemisphere and that symptoms may be alleviated by restoration of the flow.[3] Thus, the advisability of attempting to increase the volume of carotid blood flow by removing an atheromatous plaque from the carotid bulb arises often in the management of patients with cerebral circulatory insufficiency.

Just as has been demonstrated that carotid flow on one side can be sacrificed surgically in many patients without causing a neurologic deficit, it now is evident that an internal carotid artery commonly becomes occluded completely by atheromatous plaques without having caused manifestations of cerebral ischemia. On the other hand, a major stroke may seem to be due to an atheromatous plaque of the carotid bulb although the obstruction is only partial. Even more paradoxical are some patients in whom minor or major strokes develop without angiographic evidence of organic obstruction of the carotid or cerebral arterial trees. It is obvious that there is tremendous individual variation in the response to interference with the carotid blood flow as judged by evidence of cerebral ischemia or failure of such evidence to appear. The general conclusion that apparently may be deduced from these and other divergent

*Read before the Section on Neurology and Psychiatry, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

†From the Section on Neurosurgery, Ochsner Clinic and the Departments of Surgery (Section on Neurosurgery) and Anatomy, Tulane University School of Medicine, New Orleans, La.

Supported in part by a grant from the Louisiana Heart Association.

reactions to interference with carotid blood flow is that, although we all become more vulnerable to additional interference with the cerebral circulation as we become older, some must have an unusually greater congenital vulnerability to such an interference with the blood supply to the cerebrum.

Alternate compression of the carotid systems in the neck is the method most often used to evaluate the patient's degree of dependence upon each carotid blood flow. Failure of the patient to tolerate such compression may be indicative of a hyperactive carotid sinus reflex rather than that the cerebrum is functioning on a narrow margin of safety relative to its circulation. However, it seems evident now that the syndrome of the hyperactive carotid sinus reflex is rare. Tolerance to obstruction of the carotid flow by external compression may mean that the flow was not blocked completely or that complete obstruction was not maintained for a sufficiently long period. Auscultation over the carotid vessels in the neck and ophthalmodynamometry are other aids in evaluation of the status of the carotid blood flows.

Bilateral carotid angiography is essential for adequate evaluation of a patient suspected of having an intracranial aneurysm or a stroke secondary to regional ischemia. These studies are done primarily to learn more regarding the nature and location of the etiologic lesion. Carotid angiography should be performed bilaterally in both types of cases to determine whether other significantly obstructive lesions or other aneurysms are present. In addition, much valuable information can be obtained concerning the prognosis with regard to development of a neurologic deficit if the carotid flow on one side is sacrificed in the treatment of an aneurysm, or if endarterectomy is deferred when minor strokes due to an atheromatous plaque of the carotid bulb are occurring.

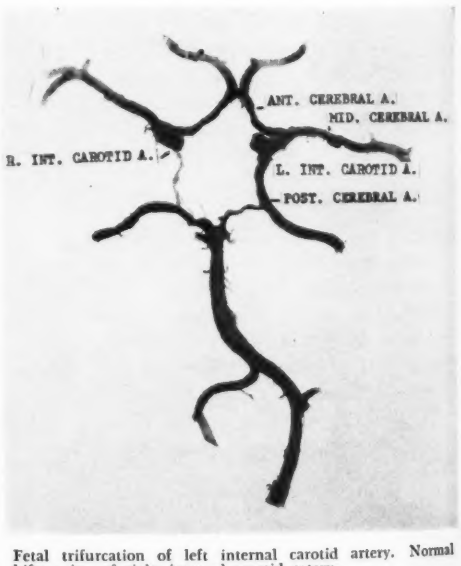
Anatomic Considerations

An unusual degree of dependence of the cerebrum upon carotid blood flow on a congenital basis generally is due to the fact that the internal carotid artery supplies blood to the areas of distribution of three major cerebral arteries rather than two, as in the case of its normal bifurcation.[4] These instances thus constitute a form of functional trifurcation of the internal carotid artery. There are three principal forms of functional trifurcation of the internal carotid artery: fetal trifurcation, transitional trifurcation and anterior trifurcation.[5] The anatomic characteristics of each type and the associated modifications in the circle of Willis are as follow:

(a) *Fetal trifurcation* consists of persistence of the early fetal pattern of branching of the internal carotid artery in which all three major cerebral arteries arise from the internal carotid artery (Fig. 1). The posterior cerebral segment of the ipsilateral side of the circle of Willis is a slender vessel similar to the posterior communicating artery of the normal circle. Thus, with obstruction of this internal carotid artery a minimal volume of collateral flow would occur from the vertebral-basilar system.

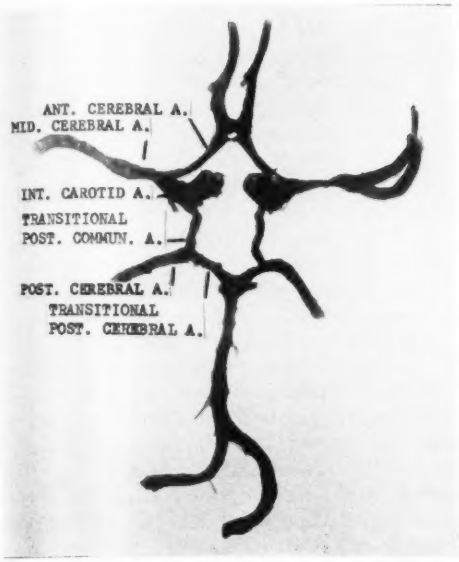
(b) *Transitional trifurcation* results from arrest at some stage of the transition of the large posterior communicating branch of the early fetal circle to its attenuated normal adult form (Fig. 2). Simultaneous with this arrest is arrest of the transition of the posterior cerebral segment of the early fetal circle to its relatively large normal adult size. Thus, with transitional trifurcation of the internal carotid artery, the posterior communicating

FIG. 1



Fetal trifurcation of left internal carotid artery. Normal bifurcation of right internal carotid artery.

FIG. 2



Transitional trifurcation of both internal carotid arteries. Note the relationship in size of each posterior communicating segment of the circle to the corresponding posterior cerebral segment and the posterior cerebral artery distal to the circle.

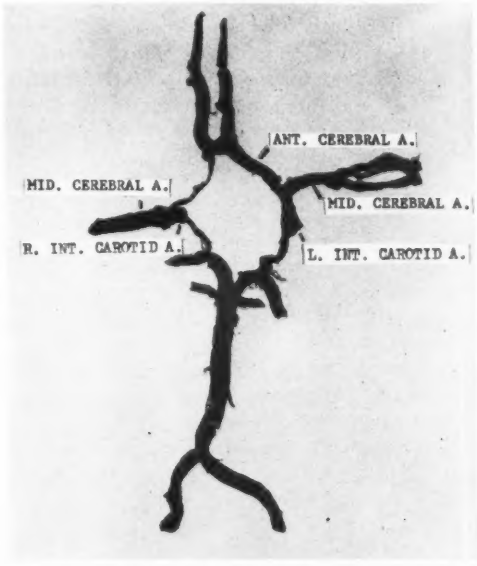
and the posterior cerebral segments of the ipsilateral side of the circle of Willis have an inverse relationship in size compared with the size of the posterior cerebral artery distal to the circle.

With occlusion of this type of internal carotid artery the normal volume of collateral blood flow from the vertebral-basilar system is reduced. However, owing to the comparatively large posterior communicating artery, a relatively large portion of the collateral flow would pass directly into the carotid system, and thus its peripheral distribution undoubtedly would be more effective than in the case of carotid occlusion with a normal circle.

(c) *Anterior trifurcation* consists of division of the internal carotid artery into a middle cerebral artery and an unusually large anterior cerebral artery (Fig. 3). The latter divides at the anterior margin of the circle of Willis into both anterior cerebral arteries. Thus, the trifurcated artery supplies the usual area of distribution of the internal carotid artery in the ipsilateral cerebral hemisphere, plus the usual area of distribution of the anterior cerebral artery in the opposite hemisphere. This type of trifurcation of the internal carotid artery always is accompanied by an anomaly of the opposite internal carotid artery. The anterior cerebral segment of the opposite side of the circle is an attenuated vessel or is missing. If an internal carotid artery with anterior trifurcation is occluded, both frontal lobes are deprived of their direct blood supply. If the artery supplies the dominant cerebral hemisphere, all of the ipsilateral motor and sensory cortex as well as the motor speech area and the important association areas of the superior temporal gyrus and the temporoparietal area also lose their direct blood flow.

Anterior trifurcation of one internal carotid artery usually is accompanied by reverse bifurcation of the opposite internal carotid. However, the latter artery may fail to bifurcate but continues as the middle cerebral artery. With reverse bifurcation the posterior branch, which is the functional posterior cerebral artery, is joined to the basilar artery only by an attenuated vessel. Thus, the internal carotid arterial tree with reverse bifurcation is relatively isolated from the vertebral-basilar system as is the case with fetal trifurcation.

FIG. 3



Anterior trifurcation of left internal carotid artery. Right internal carotid artery continues as middle cerebral artery.

reactions to interference with carotid blood flow is that, although we all become more vulnerable to additional interference with the cerebral circulation as we become older, some must have an unusually greater congenital vulnerability to such an interference with the blood supply to the cerebrum.

Alternate compression of the carotid systems in the neck is the method most often used to evaluate the patient's degree of dependence upon each carotid blood flow. Failure of the patient to tolerate such compression may be indicative of a hyperactive carotid sinus reflex rather than that the cerebrum is functioning on a narrow margin of safety relative to its circulation. However, it seems evident now that the syndrome of the hyperactive carotid sinus reflex is rare. Tolerance to obstruction of the carotid flow by external compression may mean that the flow was not blocked completely or that complete obstruction was not maintained for a sufficiently long period. Auscultation over the carotid vessels in the neck and ophthalmodynamometry are other aids in evaluation of the status of the carotid blood flows.

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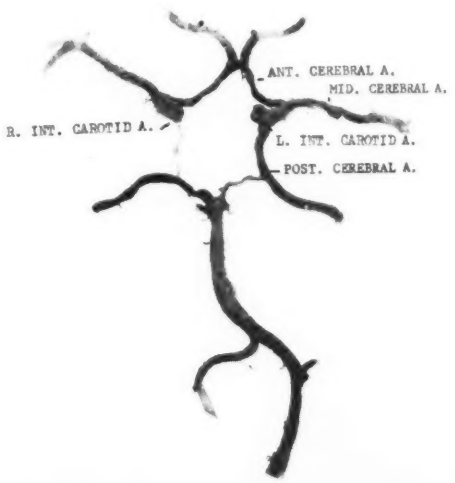
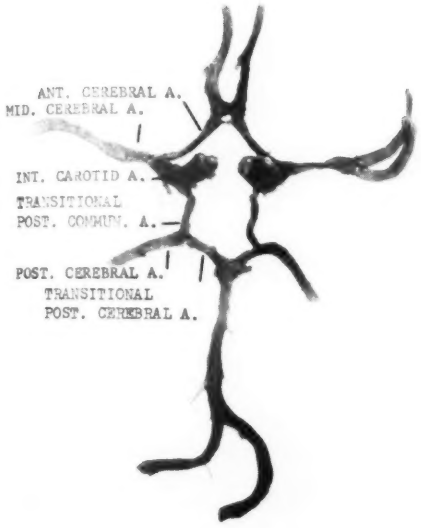


Fetal trifurcation of left internal carotid artery. Normal bifurcation of right internal carotid artery.

FIG. 2



Transitional trifurcation of both internal carotid arteries. Note the relationship in size of each posterior communicating segment of the circle to the corresponding posterior cerebral segment and the posterior cerebral artery distal to the circle.

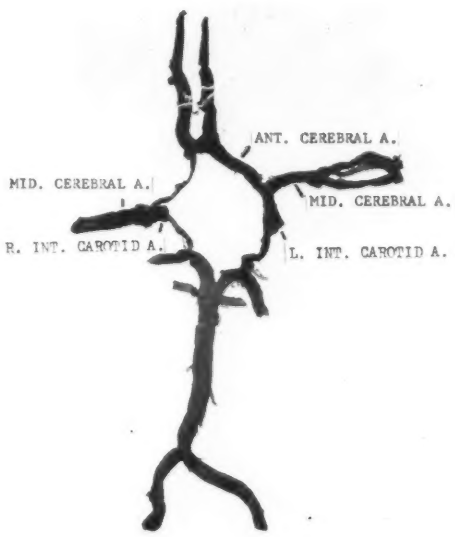
and the posterior cerebral segments of the ipsilateral side of the circle of Willis have an inverse relationship in size compared with the size of the posterior cerebral artery distal to the circle.

With occlusion of this type of internal carotid artery the normal volume of collateral blood flow from the vertebral-basilar system is reduced. However, owing to the comparatively large posterior communicating artery, a relatively large portion of the collateral flow would pass directly into the carotid system, and thus its peripheral distribution undoubtedly would be more effective than in the case of carotid occlusion with a normal circle.

(c) *Anterior trifurcation* consists of division of the internal carotid artery into a middle cerebral artery and an unusually large anterior cerebral artery (Fig. 3). The latter divides at the anterior margin of the circle of Willis into both anterior cerebral arteries. Thus, the trifurcated artery supplies the usual area of distribution of the internal carotid artery in the ipsilateral cerebral hemisphere, plus the usual area of distribution of the anterior cerebral artery in the opposite hemisphere. This type of trifurcation of the internal carotid artery always is accompanied by an anomaly of the opposite internal carotid artery. The anterior cerebral segment of the opposite side of the circle is an attenuated vessel or is missing. If an internal carotid artery with anterior trifurcation is occluded, both frontal lobes are deprived of their direct blood supply. If the artery supplies the dominant cerebral hemisphere, all of the ipsilateral motor and sensory cortex as well as the motor speech area and the important association areas of the superior temporal gyrus and the temporoparietal area also lose their direct blood flow.

Anterior trifurcation of one internal carotid artery usually is accompanied by reverse bifurcation of the opposite internal carotid. However, the latter artery may fail to bifurcate but continues as the middle cerebral artery. With reverse bifurcation the posterior branch, which is the functional posterior cerebral artery, is joined to the basilar artery only by an attenuated vessel. Thus, the internal carotid arterial tree with reverse bifurcation is relatively isolated from the vertebral-basilar system as is the case with fetal trifurcation.

FIG. 3



Anterior trifurcation of left internal carotid artery. Right internal carotid artery continues as middle cerebral artery.

Carotid Angiograms Indicative of Unusual Congenital Intolerance to Interference with Carotid Blood Flow

(a) *Fetal Trifurcation.* The angiographic picture of persistence of the early fetal pattern of trifurcation of the internal carotid artery consists of demonstraion of a posterior communicating branch of the internal carotid artery which is the size of a posterior cerebral artery, in addition to middle and anterior cerebral arteries of normal size. This anomalous pattern of branching of the internal carotid artery usually is identified angiographically with greatest certainty on the lateral projections of the skull, but it may be evident on the anteroposterior projections. Without exception this pattern of branching of the internal carotid artery is accompanied by an attenuated posterior cerebral segment of the circle of Willis which eliminates practically all of the blood flow, except for an extremely small proportion of the usual volume of collateral blood flow deriving from the vertebral-basilar system, when the direct carotid flow to the hemisphere is obstructed. If such a patient had unusually efficient alternate routes for collateral circulation to the affected hemisphere, it seems possible that extensive cerebral softening might not develop at once. However, although we have been impressed by the ability of the cerebrum to continue to function with comparative normalcy in spite of gross reduction in its normal blood flow, it appears highly probable that a cerebral hemisphere so isolated from the heart would at least gradually undergo atrophic changes because of relative ischemia even though immediate catastrophic softening did not occur.

(b) *Transitional Trifurcation.* There are many variations of transitional trifurcation of the internal carotid artery, since the transitional changes in the posterior communicating and the posterior cerebral segments of the circle of Willis that characteristically occur during fetal development may become arrested at any point. These variations are evident on the carotid angiogram in the size of the posterior communicating artery. If this vessel is larger than the normal posterior communicating artery but smaller than the posterior cerebral artery distal to the circle of Willis, one knows that transitional trifurcation is present and that the volume of collateral flow from the vertebral-basilar system upon occlusion of the internal carotid artery will be less than normal. Since the posterior communicating and posterior cerebral segments of the circle of Willis have an inverse relationship in size as compared with the posterior cerebral artery distal to the circle, the potential for collateral flow from the vertebral-basilar system can be estimated from the angiogram.

(c) *Anterior Trifurcation.* This anomalous pattern of branching of an internal carotid artery is suggested angiographically by visualization of both anterior cerebral arteries in addition to the ipsilateral middle cerebral artery. Since visualization of the contralateral anterior cerebral artery in the carotid angiogram is more often the result of some interference with the normal blood flow through the contralateral carotid system, or with the unusually forceful injection of the radiopaque substance, carotid angiography must be done bilaterally to establish the diagnosis of anterior trifurcation of this artery. With anterior trifurcation of one internal carotid artery, carotid angiography on the opposite side will demonstrate the posterior and middle cerebral arterial trees, or a small posterior communicating artery and the middle cerebral arterial tree, but the anterior cerebral artery usually is not visualized in either instance.

Tolerance of a patient to interference with blood flow through an internal carotid system with anterior trifurcation must be greater than with fetal trifurcation, because there will be a normal volume of collateral flow from the vertebral-basilar system, barring some organic change such as a strategically placed atheromatous plaque. However, with reverse bifurcation of the opposite internal carotid artery, that arterial tree is relatively isolated from the vertebral-basilar system in the same manner as with fetal trifurcation. Therefore, with interference in the blood flow through the trifurcated artery, there is less collateral flow available from the contralateral carotid system if that internal carotid artery bifurcates rather than continuing as a single vessel, the middle cerebral.

Angiographic Evidence of Critical Intolerance to Further Interference with Carotid Flow due to Organic Changes

1. *Complete Obstruction of Internal Ca-*

rotid Artery. Carotid angiography may demonstrate, anatomically, normal arterial trees, but may reveal atheromatous lesions that would suggest a severe neurologic deficit would develop if any further interference with the carotid flow occurred. There is general agreement that bilateral carotid angiograms are essential in the evaluation of every patient with cerebral circulatory insufficiency, in whom surgical treatment is contemplated as well as in cases of intracranial aneurysm. They are particularly important, however, in those patients whose internal carotid artery on the side of the ischemic hemisphere is found to be occluded completely. This is true because it is not unusual to find that the patency of this artery cannot be re-established when the obstruction is complete, because of fibrotic changes in the distal segment. Furthermore, it may be apparent that the patient had tolerated loss of the direct ipsilateral carotid flow and finally presented evidence of cerebral ischemia when loss of the opposite carotid flow became imminent. Endarterectomy of the partially obstructed vessel may cause complete freedom from symptoms.

2. *Partial Obstruction of Internal Carotid Artery.*

(a) With Incomplete Filling of Distal Segment. At angiography, the contrast medium may pass a large atheromatous plaque of the carotid bulb but only irregularly outline the distal segment of the artery. The intracranial portion of the involved arterial tree may not be visualized so that any unusual intolerance, on a congenital basis, to complete loss of the affected carotid flow cannot be evaluated. Of course, this may be predicted by the current neurologic status, by the response to unilateral compression of the carotid flows and by the results of ophthalmodynamometry. We believe this is the angiographic picture in which there often is a soft clot in the distal segment of the artery which may be extruded spontaneously by the collateral flow or may be removed by gentle suction.

(b) With Complete Filling of Distal Segment and Visualization of Intracranial Branches. Adequate visualization of the entire arterial tree distal to the etiologic lesion allows one to indicate the prognosis with somewhat greater certainty than if the pattern of branching of the affected artery is not known. However, the possibility for re-establishing relatively normal direct flow in this situation by endarterectomy is so great that only definite contraindication to surgical treatment, because of disease elsewhere, would seem to justify deferring this definitive treatment, even though angiographic evidence for an adequate collateral circulation was demonstrated.

Summary

The most common congenital anomalies of the vascular tree, evident on carotid angiography, which may indicate that a patient will not tolerate loss of internal carotid blood flow, are fetal trifurcation, anterior trifurcation and reverse bifurcation of the internal carotid artery in question. There are many combinations of atheromatous lesions of the carotid and cerebral arterial trees, or of atheromatous lesions and congenital anomalies, which may indicate an unfavorable prognosis if the patient presents a history suggesting transient regional cerebral ischemia, or if the direct carotid blood flow to one cerebral hemisphere is occluded in the treatment of a ruptured intracranial aneurysm. A comparatively common angiographic observation in patients with cerebral ischemia is that both carotid bulbs contain large atheromatous plaques. In such cases, the prognosis without endarterectomy would seem unfavorable, regardless of the pattern of branching of the internal carotid artery supplying the hemisphere to which the neurologic symptoms are referable. Since the problem of insufficiency of the cerebral circulation usually involves older patients, correlation of the carotid angiograms and the clinical picture generally requires consideration of both congenital anomalies and atheromatous lesions. The observations regarding anomalous anatomic patterns of the circle of Willis are representative of the more unfavorable prognoses relative to cerebral circulation that may be indicated by carotid angiography. The clinical course in any case can be evaluated most accurately only by correlation of the neurologic and general clinical observations with the results of such tests as alternate compression of the carotid flow, palpation and auscultation of the carotid pulses, electroencephalography, ophthalmodynamometry, cerebrospinal fluid studies and angiography.

References

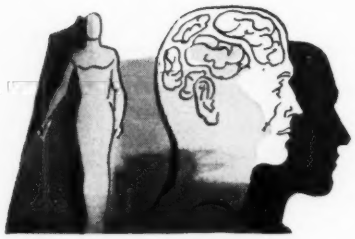
1. Rogers, L.: Ligation of the Common Carotid Artery. Report of 19 Personal Cases, Lancet 1:949, 1949.
2. Fager, C. A.: The Effectiveness and Risk of Carotid Ligation in the Treatment of Intracranial Aneurysms, Lahey Clin. Bull. 10:226, 1958.
3. Webster, J. E., Gurdjian, E. S., and Martin, F. A.: Carotid Artery Occlusion, Neurology 6:491, 1956.
4. Kirgis, H. D., Peebles, E. McC., Ebbesson, S. O., and Matthews, G. N.: The Functional Significance of Variations in the Anatomy of the Major Arteries at the Base of the Brain, Anat. Rec. 133:451, 1959.
5. Kirgis, H. D., Llewellyn, R. C., and Peebles, E. McC.: Trifurcation of the Internal Carotid Artery and Its Potential Clinical Significance, J. Neurosurg. 17:1062, 1960.

Discussion (Abstract)

Dr. R. Eustace Semmes, Memphis, Tenn. Early in the development of neurosurgery of the cerebral circulation it became evident that, for adequate evaluation, it was necessary to study not only the vessel involved but also the condition of the contributing and collateral vessels. The cerebral vascular system is inherently complex, and anatomic variations are commonly encountered, which complicate the picture still further. Doctor Kirgis has presented this important aspect of the subject very comprehensively and clearly. The schematic illustrations are remarkably well done. The publication of this paper will materially assist all of us in the study of these cases and in determining when surgical interference is indicated and when it would be useless or harmful.

The risk and complications of cerebral arteriography have just been brought up. Our series of 1,700 cases, including 3,196 vessel injections, has just been reviewed. There was a mortality of 0.4% and there were complications of some sort in 2.5 per cent. The percutaneous method was used with local anesthesia.

It must be remembered, of course, that the blood supply to the brain is also influenced by the level of the blood pressure, the caliber and elasticity of the vessels, and the oxygen content and viscosity of the blood, as well as the presence of arteriospasm. The time element in occlusion is of great importance in allowing opportunity for development of adequate collateral circulation.



The Dysproteinemias*

WADE VOLWILER, M.D.,† *Seattle, Wash.*

Alterations in the plasma proteins are not uncommonly encountered as a manifestation of disease. The changes may be either quantitative or qualitative. Dysproteinemia may be the result of disturbances in synthesis, catabolism, distribution within the body or external loss of plasma proteins. Frequently, combinations of these factors may occur simultaneously.

ACCORDING TO ITS DERIVATION, the word dysproteinemia literally means an abnormality of the proteins of the blood. However, custom restricts the application of the term to disorders of the proteins of plasma.

Three general kinds of dysproteinemia are recognized: (1) A gross change in the total concentration or amount of plasma proteins without proportionate change of the ingredients. Probably the best example of this type is the simple hypoproteinemia resulting from massive hemorrhage. (2) A gross quantitative disproportion among the normal components of the plasma proteins, due to gross increases or decreases of individual major components. (3) A gross qualitative abnormality in the varieties of plasma proteins present. This may be due either to, (a) virtual absence of a normal major component, or (b) the appearance of large amounts of an unusual protein not ordinarily identified among normal plasma proteins; the latter is termed a paraprotein.

Bodily disturbances which lead to dysproteinemias lie within the 4 general mechanisms which always determine the concentration of proteins in plasma: The processes of synthesis, destruction, internal bodily distribution (or dilution) and external loss. The concentration of a given protein in plasma is the net result of all of these simultaneously operating processes. Frequently, disturbances of more than one of these general mechanisms may exist at the same time in the same patient.

I. Disturbances in Manufacture

The number of grams of each plasma protein made daily is determined by the total activity of a specific synthesizing enzyme system. The degree of this activity depends upon (a) the number of such synthetic machines active, and (b) the rate at which they produce. The rate of activity of each unit is influenced by circulating chemical accelerators and inhibitors, by genetic factors, and by the availability of raw materials.

The number of manufacturing units is likely to vary in proportion to the cellular mass of the organs containing them. Thus, marked destruction of an organ primarily responsible for producing a specific plasma protein would result in a decreased daily synthesis of this plasma component. Examples of this type of defect are, (a) the decreased rate of production of albumin in the shrunken liver of advanced portal cirrhosis, and (b) the almost complete absence of production of gamma globulins in syndromes of agammaglobulinemia, wherein there is a virtual absence of plasma cells.[1]

In contrast, a marked increase in the mass of a bodily organ system may result in an increased rate of production of a single kind of plasma protein made by its excessive number of cells. Examples of this kind of defect are found in virtually all of the hypergammaglobulinemias, due to expansion of the body's plasma cell mass. At least 3 types are recognized: (a) In standard varieties of inflammation, there is ordinarily an increase in the total number of plasma cells. The increased daily production of gamma globulins spans the usual broad electrophoretic range of the gamma globulins. (b) In response to a specific bacterial type antigen, the plasma cell mass may also increase. The increase in gamma globulins resulting is especially antibody specific to the injected antigen. (c) In malignant diseases of the reticuloendothelial system, the

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infiltrating abnormal cells may produce and deliver to the circulation abnormal globulins or paraproteins. As a specific example, in multiple myeloma, massive numbers of malignant plasma cells appear. These may produce daily a huge amount of an abnormal plasma globulin, which is individually characteristic for each patient.[2] The homogeneity of the molecular species of the paraprotein is reflected in the very narrow band observed in paper electrophoretic patterns, as contrasted with the broad band of increased gamma globulins of many molecular species found in the hypergammaglobulinemias of (a)[3-6] (Fig. 1). Examined by ultracentrifuge, these myeloma proteins have sedimentation constants of 7, and are of the general molecular size usual for the bulk of normal gamma globulins.[7]

In another malignant reticuloendothelial disorder, Waldenström's macroglobulinemia, there occurs massive infiltration into bone marrow of a slightly different pathologic cell, intermediate in many of its morphologic characteristics between small lymphocyte and plasma cell. These cells produce and deliver into the circulation a paraprotein of very large molecular mass denoted by the very high sedimentation constant of 19. For each patient, the exact composition of this paraprotein is also individually characteristic.[8] All such macroglobulins which have been studied carefully have been shown to be composed of polymers the size of normal gamma globulins.[9] However, these polymeric units have been determined to be somewhat different from normal gamma globulins as regards amino acid sequences.

FIG. 1

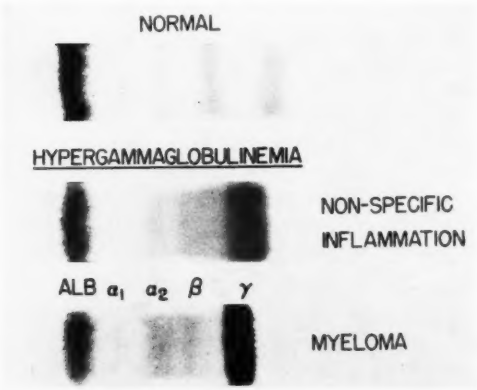


FIG. 2

PARAPROTEINEMIAS

Myeloma "Mesa"-globulinemia Macro-globulinemia

Intermediate between the classic syndromes of myeloma and Waldenström's macroglobulinemia lie a group of unsual reticuloendothelial disorders. In these conditions, the bone marrow is infiltrated with varying combinations of normal or atypical plasma cells and/or strange lymphocytes. These cell types produce pathologic proteins intermediate in mass size, with ultracentrifuge sedimentation constants between 8 and 14 ("mesaglobulins"). A typical serum ultracentrifuge pattern of this condition is provided in figure 2. The associated clinical syndromes are composed of varying combinations of the features of classic myeloma and macroglobulinemia.

Each of these 3 varieties of paraproteinemia —myeloma, "mesaglobulinemia," and macroglobulinemia—probably represents segments of a broad spectrum of one general malignant disorder of the reticuloendothelial system.

Regardless of all other factors, the pace of synthetic activity for plasma proteins will finally be determined by the availability of raw materials (amino acids) for their manufacture. Fortunately, the mammalian body exhibits important rules of homeostasis in its protection of the plasma protein stores. Even during periods of starvation, the destruction of bodily tissues furnishes to the amino acid pool sufficient ingredients to satisfy the high priority of demand to manufacture plasma proteins. The question has recurringly been raised as to the relative priority in competition for these raw materials to make the various individual plasma proteins.

Is there priority for making one type of plasma protein over another? Presumably, each kind is made by its own individual enzyme system. Although each such manufac-

turing unit must compete for raw materials from the same bodily amino acid pool, it seems unlikely that the units are otherwise interdependent in their pace of activity. In this connection, the old alleged significance of the A/G ratio—that there is a usual and necessary dependent reciprocity in the rate of production of globulins to albumin—appears invalid in most clinical situations. In the bulk of dysproteinemias, the principal factors determining the proportionate plasma concentration of individual components are independently concerned with the production, distribution and destruction of specific proteins. There are usually enough amino acids in the amino acid pool to satisfy the needs of all synthetic units. Only when there is extraordinary stimulus to produce a massive amount of one specific variety of plasma protein may the manufacture of other proteins suffer as a direct result of the shunting of amino acids to greedy specific cell types. Most commonly, this phenomenon is observed when there is massive expansion of the plasma cell mass, as in some cases of malignant myeloma.

II. Disturbances in Catabolism

Evidence has accumulated to indicate that the plasma proteins participate in the general laws of bodily protein catabolism. Thus, those processes which increase generally the rate of destruction of body tissue proteins are accompanied also by an increased rate of destruction of the circulating plasma proteins. It has been specifically demonstrated that administration of thyroid or of certain adrenal cortical hormones can increase the rate of bodily catabolism of albumin;[10-12] presumably, the influence of the same agents upon the rate of destruction of other plasma proteins is similar.

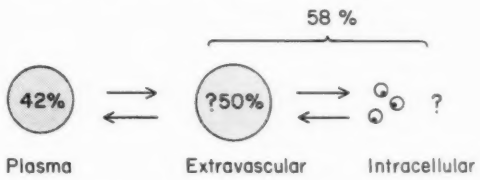
The total life span in the body of a specific plasma protein is a measure of its rate of catabolism. The life spans of specific normal plasma proteins in the normal adult human[13] are approximately as follows:

	Half-life ($t_{\frac{1}{2}}$) *(Days)*	*Total Life (T) (Days)*
Albumin	14 – 23	33
Gamma globulins	10 – 35	50
Prothrombin	0.7	1
Fibrinogen	3 – 5	4 – 7
β-lipoprotein	2.5 – 3.5	3.5 – 5

These values must be considered as crude approximations. Present-day technics for their determination are not precise.[13] A broad biologic range for the normal exists for the life span of each molecular species.

FIG. 3

BODY POOL OF PLASMA PROTEINS



When these normal rates of destruction become altered by disease, the body usually attempts to compensate by an appropriate adjustment in rate of production, with the purpose of maintaining homeostasis. To maintain constancy, the rate of production of a given plasma protein must keep pace with the rate of its destruction.

III. Disturbances in Bodily Distribution

The various plasma proteins circulate and exchange among all of the body's tissue fluid pools, even including cerebrospinal fluid. Moreover, certain of the plasma proteins (albumin) have been tentatively identified intracellularly in a wide variety of body organs.[14] Recent studies have indicated that, actually, more than half of the body's stock of circulating plasma proteins lies in fluid pools outside the rapid circulation, or "plasma space"[15] (Fig. 3). The rate of interchange of the plasma proteins between plasma and extravascular fluid varies greatly among bodily organs; such rates of exchange are characteristic for each tissue[16] and are determined in part by the submicroscopic structural arrangement of the boundaries between cells, capillaries and small lymphatics.

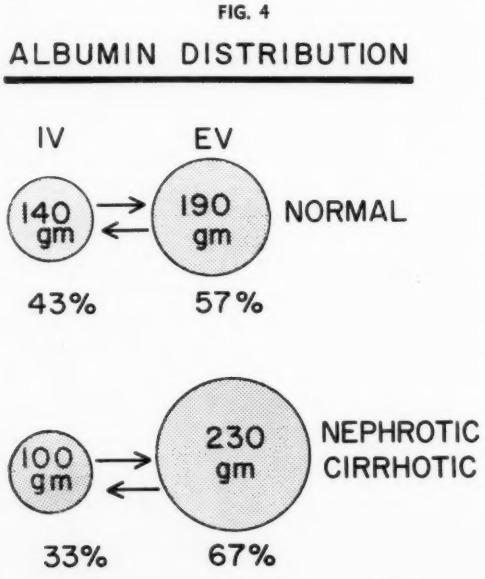
Sudden disturbances of this complex normal distribution pattern come about with the expansion or retraction of any of the groups of intravascular or extravascular fluid compartments.[17] Thus, the sudden appearance of edema fluid in a wide tissue area, or within a serous cavity may suddenly drain off a large stock of the body's plasma protein pool. Accordingly, it has been estimated that some nephrotics and cirrhotics exhibiting marked edema and/or ascites may, although hypoproteinemic by concentration of proteins in plasma, actually possess a near normal total

body plasma protein mass, which has simply been partially diverted into the expanding extravascular fluid spaces (Fig. 4).

IV. Alterations in External Losses

Small amounts of plasma proteins are regularly lost from all external surfaces. Tiny amounts are present in normal urine. Plasma proteins are normally extruded in virtually all gastrointestinal secretions, which together provide a small daily loss from the body's plasma protein pool. Exudative inflammation of any of the body's surfaces can result in a massive daily loss of plasma proteins. For skin, it has long been recognized that many grams of plasma protein may seep daily through the damaged skin of burns or of weeping exfoliative dermatitis. For the gastrointestinal tract, it has been realized for many years that considerable amounts of plasma proteins are lost during gastrointestinal hemorrhage, whether the bleeding be acute and suddenly massive, or chronically depleting, as in ulcerative inflammatory disorders of the intestines. But very recently, it has been strikingly demonstrated that neoplasm, inflammation and other structural defects of the mucosal surface of gastrointestinal organs may weep plasma without erythrocytes, and thereby result in a severe daily drain of the body's plasma protein pool.[18,19] The term exudative gastroenteropathy seems excellently appropriate to connote this feature of pathophysiology common to a host of varieties of mucosal disorders.[20]

FIG. 4



Summary

Alteration from the normal concentration of a plasma protein may have one or several explanations. In each instance, the appropriate explanation must be sought among the 4 major mechanisms which cause dysproteinemia, namely, disturbances of synthesis, catabolism, internal bodily distribution, and external loss of the plasma proteins.

Thoughtful dissection of the pathophysiology of each patient's disease should thus allow the responsible physician to explain the origin of a dysproteinemia. A logical mode of therapeutic attack would then naturally follow.

References

1. Good, R. A.: Studies on Agammaglobulinemia: II. Failure of Plasma Cell Formation in the Bone Marrow and Lymph Nodes of Patients with Agammaglobulinemia, J. Lab. & Clin. Med. 46:167, 1955.
2. Putnam, F. W.: Abnormal Human Serum Globulins: II. Physical Constants and Amino End Groups, J. Biol. Chem. 233:1448, 1958.
3. Conn, H. O., and Klatskin, G.: Filter Paper Electrophoretic Patterns of Serum in Multiple Myeloma, Am. J. Med. 16:822, 1954.
4. Osserman, E. F., and Lawlor, D. P.: Abnormal Serum and Urine Proteins in Thirty-five Cases of Multiple Myeloma, as Studied by Filter Paper Electrophoresis, Am. J. Med. 18:462, 1955.
5. Kyle, R. A., Bayrd, E. D., McKenzie, B. F., and Heck, F. J.: Diagnostic Criteria for Electrophoretic Patterns of Serum and Urinary Proteins in Multiple Myeloma, J.A.M.A. 174:245, 1960.
6. Fahey, J. L., and Horbett, A. P.: Human Gamma Globulin Fractionation on Anion Exchange Cellulose Columns, J. Biol. Chem. 234:2645, 1959.
7. Putnam, F. W.: Abnormal Serum Globulins: D. Ultracentrifugal Analysis of Serum, in The Plasma Proteins. Vol. 2, Chap. 18. Putnam, F. W., Ed. New York, Academic Press, Inc., 1960, page 358.
8. Putnam, F. W.: Abnormal Human Serum Globulins. I. The Nonidentity of Macroglobulins, Arch. Biochem. and Biophys. 79:67, 1959.
9. Deutsch, H. F., and Morton, J. I.: Human Serum Macroglobulins and Dissociation Units. I. Physicochemical Properties, J. Biol. Chem. 231:1107, 1958.
10. Rothschild, M. A., Schreiber, S. S., Oratz, M., and McGee, H. L.: The Effects of Adrenocortical Hormones on Albumin Metabolism Studied with Albumin I^{131}, J. Clin. Invest. 37:1229, 1958.
11. Rothschild, M. A., Bauman, A., Yalow, R. S., and Berson, S. A.: The Effect of Large Doses of Desiccated Thyroid on the Distribution and Metabolism of Albumin I^{131} in Euthyroid Subjects, J. Clin. Invest. 36:422, 1957.
12. Iber, F. L., Nassau, K., Plough, I. C., Berger, F. M., Meroney, W. H., and Fremont-Smith, K.: The Use of Radioiodinated Albumin in Metabolic Studies. The Effects of the Level of Dietary Protein and L-Triiodothyronine on the Catabolism of Radioiodinated Human Serum Albumin, J. Clin. Invest. 37:1442, 1958.
13. Goldsworthy, P. D., and Volwiler, W.: Comparative Metabolic Fate of Chemically (I^{131}) and Biosynthetically (C^{14}- or S^{35}-) Labeled Proteins, Ann. New York Acad. Sc. 70:26, 1957.
14. Gitlin, D., Landing, B. H., and Whipple, A.: Localization of Homologous Plasma Proteins in Tissues of Young Human Beings as Demonstrated with Fluorescent Antibodies, J. Exper. Med. 97:163, 1953.
15. Steinfeld, J. L.: Difference in Daily Albumin Synthesis Between Normal Men and Women as Measured with I^{131}-Labeled Albumin, J. Lab. & Clin. Med. 55:904, 1960.
16. Benson, J. A., Jr., Kim, K. S., and Bollman, J. L.: Extravascular Diffusion of Protein, Am. J. Physiol. 182:217, 1955.
17. Freeman, T., and Matthews, C. M. E.: Analysis of the Behavior of I^{131}-Albumin in the Normal Subject and the Nephrotic Patient, in Radioaktive Isotope in Klinik und

Forschung. Vol. 3, page 283, 1958, Fellinger, K., and Vetter, H., Eds. (Suppl. to Vol. 38 of Sonderbände zur Strahlentherapie, Vienna).
18. Citrin, Y., Sterling, K., and Halsted, J. A.: The Mechanism of Hypoproteinemia Associated with Giant Hypertrophy of the Gastric Mucosa, New England J. Med. 257:906, 1957.
19. Gordon, R. S., Jr., Mod.; Bartter, F. C., and Waldmann, T., Discus.: Idiopathic Hypoalbuminemias: Clinical Staff Conference at the National Institutes of Health, Ann. Int. Med. 51:553, 1959.
20. Gordon, R. S., Jr.: Exudative Enteropathy. Abnormal Permeability of the Gastrointestinal Tract Demonstrabie with Labeled Polyvinyl Pyrrolidone, Lancet 1:325, 1959.

HOTEL RESERVATION APPLICATION FORM

FOR 55th ANNUAL SESSION

DALLAS, TEXAS, NOVEMBER 6-9, 1961

APPEARS IN THIS ISSUE

MAKE YOUR RESERVATION NOW!

Conservative Surgery for Large Ovarian Cysts*

PHIL C. SCHREIER, M.D., and ALBERT M. ALEXANDER, M.D.,†
Memphis, Tenn.

The authors point to the salvage or saving of ovarian tissue by resection of large ovarian cysts and reconstituting a functional ovary, whose importance cannot be minimized in a young woman.

THE OCCURRENCE OF DERMOID CYSTS is most common in young women and constitutes approximately 15% of all ovarian tumors which come to operation. Furthermore, 15 to 20% of these will be bilateral. Thus, since this occurs in the childbearing age it has been referred to in some of our standard texts as one of the great tragedies of gynecologic surgery.

A most satisfying experience was the discovery of the monograph, now out of print, by Dr. Victor Bonney,[1] an eminent gynecologist of England, on the removal of dermoid cysts with the conservation of ovarian tissue, in such a manner that he could say it is never necessary to remove the ovary because of an uncomplicated dermoid cyst *per se*.

In approximately 60% of cases, dermoid cysts can be recognized preoperatively by one of several diagnostic means. Positive diagnosis can be made when plain x-ray film of the abdomen reveals calcification in the area of the cyst. Another roentgenologic diagnostic sign, described as indicative of a dermoid, is an area of increased translucency representing the sebaceous contents of the cyst surrounded by a coronal density which represents the fibrous capsule. A presumptive diagnosis of dermoid cyst may often be suggested by its location anterior to the broad ligament. The fact that the x-ray does not reveal a positive diagnosis of a dermoid cyst, of course, does not exclude the possibility of its presence. A cystic tumor is usually recognized either on routine pelvic examination or coincident with some minimal pelvic pain possibly associated with partial twisting of its long pedicle, or pressure symptoms. Since it is a nonfunctioning tumor it is not associated with menstrual aberration and therefore can be distinguished from the more serious functioning tumors of the ovary. However, we believe it is wise, when operating on ovarian tumors in young women, to have a pathologist in consultation at the operating table, for his daily contact with these problems enhances his diagnostic acumen of the gross pathology. If there is doubt as to the benign nature of the cyst or tumor it may be necessary to perform the technic herein described, and have an evaluation of a frozen section of the tumor.

Removal of Dermoid Cysts by Cystectomy

Our enthusiasm for the procedure of cystectomy rather than oophorectomy stems from the first patient in our series. This was a 19 year old woman who had had a left

FIG. 1

Large ovarian cyst with no gross evidence of ovary present. Entire ovary can be salvaged.

*Read before the Section on Gynecology, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

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oophorectomy for a dermoid at the age of fifteen. She now presented herself with a dermoid in the remaining ovary which to all intents and purposes required oophorectomy as there was no gross evidence of normal ovarian substance. In the more than 5 year follow-up, it has been very gratifying to see this young woman continue her normal ovarian functions.

To illustrate another variation of the problem, a patient presented herself with a 6 months pregnancy and an impacted cyst in the cul-de-sac producing pain. At operation this was found to be a large dermoid cyst and in the upper right abdomen above the fundus the other ovary was seemingly completely replaced by two cysts, one of which was a dermoid and the other a simple cystoma. Both ovaries were conserved and the pregnancy went to term. Since that time she has had another successful pregnancy.

In another young nulligravida, a dermoid cyst was diagnosed preoperatively in one ovary. The opposite ovary at operation was found to be replaced by a 10 cm. cystoma. Neither ovary would ordinarily have invited conservatism, but by the technic of resection and reconstruction both ovaries were preserved. We have now utilized this technic in more than 50 cases of large ovarian cysts.

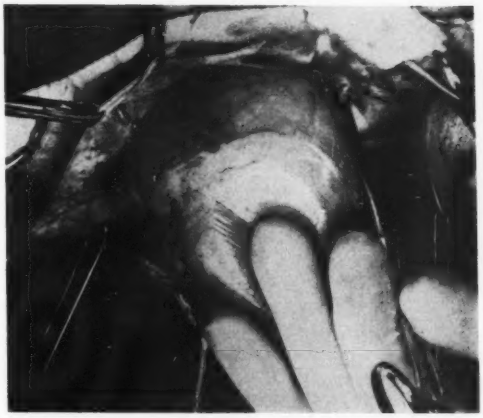
In figure 1 we see a large cyst in which there is no recognizable ovary present at original inspection, even at the hilus. This cyst had been diagnosed preoperatively as a dermoid because of opacity within its depth. The technic of cystectomy is shown by the following steps.

The cyst is completely packed off from the abdominal contents because of possible spillage should there be accidental perforation of the cyst wall. The initial incision is made at a point most distal to the hilus and Metzenbaum scissors are used to begin the dissection between the capsule of the dermoid cyst and the ovarian tissue (Fig. 2). When a wide enough area of incision is attained a moistened index finger can be used to very gently

FIG. 2

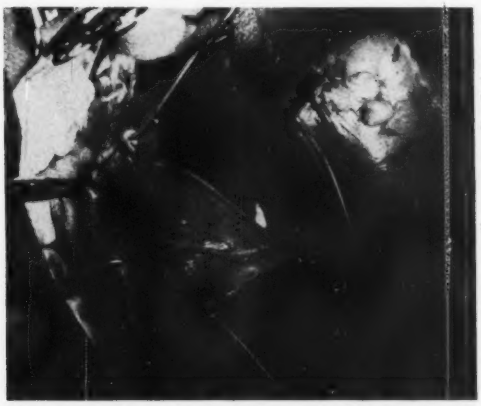
Dissection is begun at a point distal to the hilus. The incision is made through the ovarian capsule only.

FIG. 3



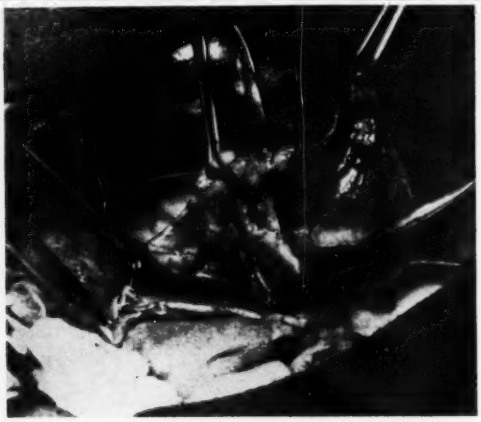
Ovarian shell partially separated from dermoid wall.

FIG. 4



Complete ovarian shell is demonstrated with excised cyst adjacent to it.

FIG. 5

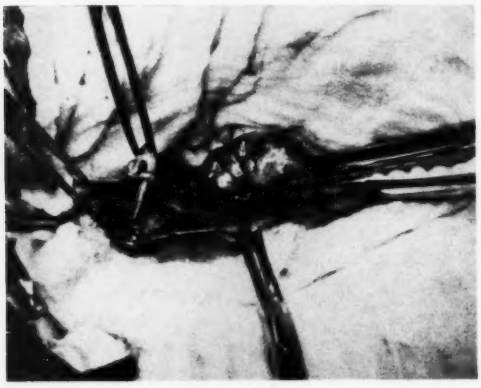


More ovarian substance than was originally seen is revealed.

shell the cyst from its ovarian base. The dissection is carried from the distal point toward the hilus on either side of the cyst for it is at the hilar area that bleeding will be encountered (Fig. 3). After the cyst is completely removed, as illustrated in figure 4, the bleeding points in the hilar base can be located and ligated without interfering with the major blood supply to the thin ovarian shell.

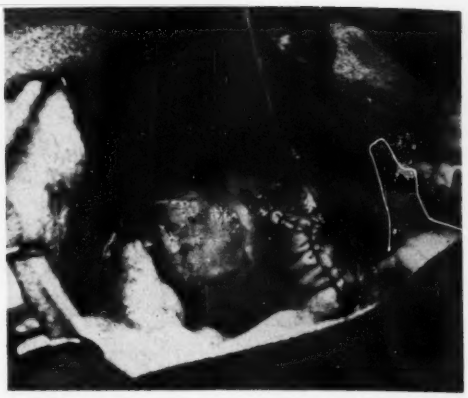
It will be noted in figure 5 that the cyst has been removed, and the epithelial surface is inspected. Much more recognizable ovarian tissue is apparent than would be suspected from this thin sheet of tissue encompassing the dermoid cyst. When the cyst was *in situ* the ovarian tissue was so compressed as not to

FIG. 6



Ovary partially reconstructed using one side of ovarian shell.

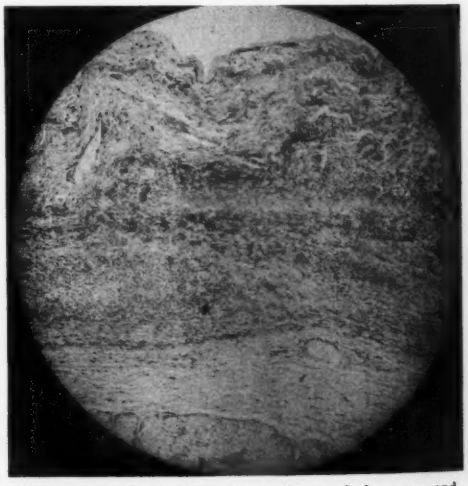
FIG. 7



Completely reconstructed ovary compared with normal left ovary.

be evident. Frequently a very sizable ovary will appear after resection of the cyst. The reconstruction is started with the enfolding of the epithelial surface of the ovary into the hilar area (Fig. 6). This enfolding of epithelial surface has not resulted with subsequent cyst formation as might be suspected on first thought of the technic. There are roughly symmetrical leaves of ovary after the initial reconstruction has been carried out so that when the two leaves have been folded into the hilar area there remain two halves of ovary which can be sutured in the midline much as following a wedge resection for poly-

FIG. 8



Photomicrograph of the entire thickness of the ovary and cyst wall showing the ovarian stroma, the capsule of the cyst, and the sebaceous glands in the lining of the cyst.

cystic ovarian disease. Figure 7 illustrates that the reconstructed ovary is quite similar to the normal ovary on the left.

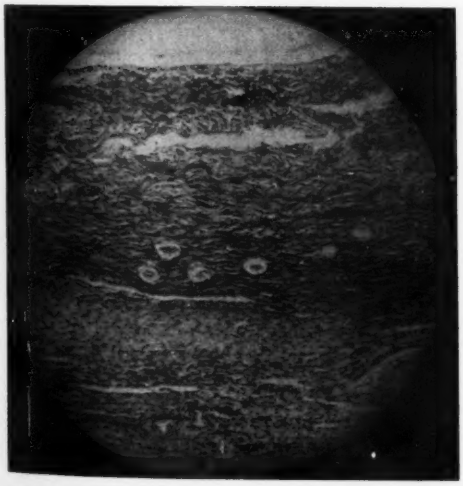
In support of the validity of this procedure a microscopic section of a dermoid cyst in which the entire ovary has been removed is presented (Fig. 8). It will be noted that the upper surface is perfectly normal ovarian stroma and at the lowermost portion there are sebaceous glands characteristic of dermoid cyst. Between these two is a fibrous capsule which is the area of our dissection. Figure 9 represents a segment of this thin ovarian tissue shell which has not only dense ovarian stroma but numerous follicles in this stroma.

Discussion

Undoubtedly many have removed small dermoids when the ovary was readily recognizable. We feel impelled to emphasize that in the absence of any recognizable ovarian tissue the technic herein described will be applicable and will result in a normal functioning ovary. Stimulated by our success in the resection of dermoids we have, as Bonney did, extended the resection to other types of benign ovarian cysts which often achieve large size.

Often associated with dermoids are other types of benign cysts, presenting a discouraging picture because of the enormity of the combined mass (Fig. 10). As a result of our experience with resection, we have extended the technic to this situation as well as to other forms of ovarian cysts.

FIG. 9



A section of the ovarian shell showing dense ovarian stroma and numerous follicles.

FIG. 10

Bilateral dermoid cysts compounded with simple cystomas. These ovaries can also be salvaged.

Should the resected cyst prove to be a papillary or pseudomucinous cystadenoma, the decision to remove the entire ovary may be indicated if it is unilateral. The balance between the possibility of malignancy and benignity is overwhelmingly in favor of cysts being benign in young women.

Although we have not met with a new or recurrent cyst in a saved ovary, it is certain there is immunity to such a development.

Conclusions

Ovaries apparently completely destroyed by large benign cysts can be conserved by resection of the cysts. This is particularly emphasized in the management of dermoid cysts of the ovary in young women, but can be applied to other varieties of cyst.

The technic of resection is described and illustrated.

The more general utilization of this simple procedure is urgently advocated.

Reference

1. Bonney, Victor: The Technical Minutiae of Extended Myomectomy and Ovarian Cystectomy. London, Paul B. Hoeber, Inc., 1946.

Discussion (Abstract)

Dr. C. P. Taylor, Ada, Okla. Three years ago I was faced with this problem of *large*, bilateral, ovarian

dermoid cysts in a 26 year old, nulliparous white woman particularly desirous of children.

The diagnosis was made prior to operation by calcarcous deposits and teeth visible on the x-ray examination of the abdomen. (Sometimes these bony deposits can be felt on examination.)

When the abdomen was opened and the cysts exposed, both were large of grapefruit size, with tightly stretched capsules so no grossly visible ovarian tissue was evident.

I had recently seen Dr. Schreier's film on the technic of resection of these cysts, and thus incised the outer layer of the capsule and shelled out the cysts without much difficulty. The large collapsed balloon-like masses of tissue remaining attached to the ovarian pedicles were folded and sutured. They resembled anything but normal appearing ovaries.

Four weeks later the patient resumed normal menstruation; within three months she was pregnant and has now borne two normal children. Recent examination revealed no ovarian enlargements and normal menstrual function continuing.

I would like to emphasize three major points brought out by Dr. Schreier concerning these cysts:

(1) The *ease* of *dissection* of the capsular layer.

(2) No ovarian tissue need be evident on gross examination.

(3) The loss incidence of recurrence and malignant change (less than 4%).

Vomiting Mechanisms: A Clinical Study of Thiethylperazine*

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The central mechanism for vomiting is not well understood, if it is to be explained on one mechanism only. Several of the newer synthetic drugs seem to have an amelioratory effect on this symptom. The authors have studied the effects of a still newer phenothiazine.

VOMITING has been an ageless problem in clinical medicine with its tendencies to appear and persist as a troublesome symptom and to falter as a protective device. Basic science studies in animals which have attempted to unscramble the neurologic and physiologic mechanisms involved in man have yielded a mixture of informative and confusing data. Innumerable noxious agents have been introduced into enteral and parenteral systems to induce emesis. Antihistaminics and closely related phenothiazine compounds have been developed in recent years to counteract vomiting. Because of the wide variety of emetic stimuli, an equally large number of antiemetic agents is accumulating rapidly.

In 1865, Gianazzi[1] reflected on the complex activity of vomiting and postulated that there might be a central mechanism for coordinating the vomiting act. However, only in the last 60 years have studies of nausea and vomiting proved enlightening.

Three evolutional phases of these studies may be described: (1) description of physiologic activity of vomiting by means of direct observations and indirect fluoroscopic methods; (2) topical destruction of various surfaces of the brain stem and cerebral cortex to permit localization of the general area of the vomiting centers; and (3) production of minute lesions to permit precise localization of the involved centers. Further studies have been hampered by differences, according to species, in neurohistologic structure of the emetic centers and in physiologic responses to various chemical agents.

Cannon,[1] in 1898, reported his observations of the activity of the stomach during digestion and vomiting by means of newly developed fluoroscopic methods. He administered apomorphine to cats after feeding them mixtures of food and bismuth compounds. At the onset of vomiting activity, the preantral portion of the stomach became completely flaccid and was separated from the antrum by a constricting ring. Following this the diaphragm flattened, and the abdominal muscles underwent quick, jerking movements, which resulted in ejection of the fundic contents into the esophagus. Only on one occasion was antiperistalsis noted during the vomiting act. Subsequent observers have verified the largely passive role of the stomach and active role of the diaphragm and abdominal muscles in emetic action. Luskiewicz,[2] who recently observed vomiting in man by fluoroscopic technics, disagreed with Cannon's observations only in his consistent observation of antiperistaltic activity in the stomach during the early stages of vomiting.

Thumas[3] was the first investigator to identify a "vomiting center." He localized it in dogs in a small midline area in the most posterior part of the rhomboid fossa. Destruction of this area eliminated the emetic response to topically applied apomorphine. Hatcher and Weiss (quoted by Borison and Wang[3]) produced the same lesion but were still able to induce vomiting by oral administration of mercuric chloride. They then destroyed the more laterally located sensory nuclei of the vagus nerve which eliminated all vomiting in their acute preparations; they concluded that this was the location of the vomiting center. Koppanyi (quoted by Borison and Wang[3]) was later able to induce vomiting by administration of mercuric

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chloride in the presence of the lesion of Hatcher and Weiss, if the animals were allowed to recover from the immediate effects of the surgical procedure. Although the primary vomiting center was not included within these destructive lesions, indications were that it was located nearby.

In 1949, Borison and Wang[3] induced vomiting in decerebrate cats by faradic stimulation through a Horsely-Clarke stereotaxic instrument and then produced localized lesions in these same regions. Histologic study of serial sections of the medulla localized the responsive points to the regions corresponding to the solitary fasciculus and nucleus and the dorsolateral border of the lateral reticular formation. The fact that these regions are situated close to the medullary vasomotor, salivation, and respiratory centers suggests the possible complex interrelationships of these various centers.

In 1951, Borison with Brizzee[3] extended the earlier work and identified an emetic chemoreceptor-trigger zone (C-T zone). This was described as an essentially non-neural zone situated between the ala cinerea and the vestibular complex, and contiguous medially with the area postrema, which overlies the ala cinerea. In the cat the C-T zone is a clear-cut morphologic entity distinct from the dorsal vagal nuclei, although in dogs it is not as distinct histologically. In the same year, Wang and Borison[3] reported a method of selectivity destroying the vomiting center while preserving the C-T zone by use of radon seed implantations (Table 1 and Fig. 1). With this preparation, they were able to ablate the emetic response to oral copper sulfate and intravenous apomorphine.

In a study of motion sickness in dogs, Wang and Chinn[3] found that the C-T zone was in the direct pathway concerned with vestibular reflex in producing motion sickness. This observation points again to the complexities of afferent pathways for vomiting.

Studies of vomiting have depended on selective interruption of probable pathways for stimuli and administration of agents known to produce vomiting by various routes and dosages. Basically, four neurologic lesions have been produced: (1) destruction of the medullary vomiting center, (2) destruction of the chemoreceptor-trigger zone, (3) interruption of vagal afferents (supradiaphragmatic or central vagotomy), and (4) total or partial sympathectomy (splanchnicectomy, high spinal cord lesions). Various combinations of these lesions have demonstrated the sites of activity of many agents (Table 1).

TABLE 1

EMETIC AGENTS

Agent	*Site of Emetic Action*
Copper sulfate, mercuric chloride i-v	C-T zone only[3]
i-g	Medullary vomiting center[3]
Apomorphine	C-T zone only[3]
Glycosides	C-T zone, unknown peripheral sites[3]
Morphine	C-T zone[3]
Hydergine	C-T zone[3]
Veratrum and its alkaloids	Nodose ganglion of vagus[3]
Nitrogen mustard	Cerebral cortex, gastrointestinal tract (cat)[3]
	C-T zone or area postrema (dog)[4,5]
Roentgen-ray irradiation	Area postrema (monkey)[4]

Wang and Borison[3] found the emetic pathways of copper sulfate to have both a peripheral and central site of action. Intragastric administration produced vomiting by impulses passing through abdominal afferents directly to the medullary vomiting center. Both the vagal and splanchnic nerves were found to

FIG. 1

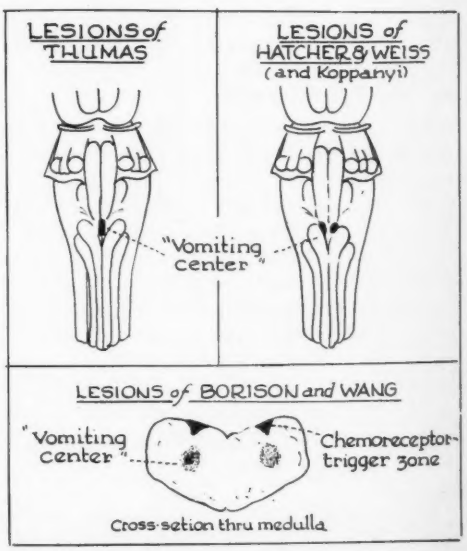


Diagram of early and current concepts of vomiting centers (courtesy of Amols and Merritt, Neurology 5:645, 1955).

be of importance, but interruption of the vagi alone had a more profound effect than total splanchnicectomy alone. With total denervation of the intestine (total sympathectomy and bilateral vagotomy), the onset of vomiting was greatly delayed, but the symptom was not abolished with intragastric copper sulfate. This suggested probable direct central stimulation when adequate blood levels of copper sulfate were produced, when earlier vomiting does not evacuate the stomach. (It has been demonstrated that total abdominal denervation does not interrupt vomiting by disturbing motor activity of the gastrointestinal tract.)[3] Ablation of the central emetic trigger zone (C-T zone) without injury to the medullary vomiting center in the animal subjected to total denervation of the intestine prevented an emetic response to lethal doses of intragastric copper sulfate. Similarly, intravenously administered copper sulfate produced vomiting only by stimulation of the C-T zone.

Apomorphine induced vomiting solely through the C-T zone by all routes of administration.[3] Gastric denervation does not alter the response to apomorphine given by any route. The emetic activity of most drugs given parenterally is mediated through this chemoreceptor-trigger zone except in monkeys,[4] in which the C-T zone generally does not respond to drugs. Monkeys fail to vomit even when given lethal doses of apomorphine. Normal cats are more refractory to apomorphine than dogs and frequently respond with states of hyperactivity instead of vomiting.[3]

Considerable difficulty has arisen during attempts to define the site or sites of action of cardiac glycosides in inducing emesis. In 1947, an attempt was made unsuccessfully to prevent glycosidic emesis by total hepatectomy and extensive denervation of the heart and all abdominal viscera. Thus, the importance of a central emetic site before its identification by more recent neurophysiologic studies was demonstrated. The work of Borison and associates[3] indicated an effect of summation of central and peripheral emetic stimuli with these drugs. They believed that emesis induced by orally administered glycosides was initiated largely by stimulation of peripheral receptors which lie outside the gastrointestinal tract (e.g., cardiac receptors). Ablation of the C-T zone prevented "early" vomiting when the glycosides were given intravenously, but did not affect the "late" vomiting if the same agent was given orally.

Morphine and Hydergine induce vomiting by acting through the C-T zone and, like apomorphine, have no enteric locus of action.[3]

Veratrum and its alkaloids apparently induce vomiting by acting at the nodose ganglion of the vagus nerve by all routes of administration in both chronic and acute preparation.[3] Neither sectioning of the vagus nerve at any point below the nodose ganglion nor decapsulation of the ganglion altered the response. However, cutting the nerve above the ganglion invariably prevented an emetic response to veriloid.

Nitrogen mustard has proved to be a potent and bewildering emetic stimulus. Other investigators were unable to prevent vomiting in cats after the administration of nitrogen mustard intravenously by chronic total denervation of the intestine with or without ablation of the C-T zone. Clamping the carotid arteries drastically reduced the incidence of vomiting among the animals, but obstruction of the thoracic aorta did not. Acute procedures of Sherrington decerebration and bilateral parietal cortical topectomy inhibited nitrogen mustard-induced vomiting, whereas extensive parietal decortication in chronic preparations did not. These workers also observed that topical application of nitrogen mustard to the parietal cortex produced vomiting, but infiltration of the same area did not. Borison and co-workers,[5] in a comparative study, found the minimum effective doses of nitrogen mustard for the production of early emesis to be 5 mg. per kilogram of body weight in cats and 0.5 mg. per kilogram in dogs. Dogs could be protected from doses of 10 mg. of nitrogen mustard per kilogram by chronic ablation of the C-T zone, whereas cats could not. Abdominal deafferentation accomplished by transthoracic vagotomy and total sympathectomy completely protected cats.

The emetic pattern elicited by roentgen-ray irradiation is similar to that of nitrogen mustard in that an "early" emetic response occurs within 4 hours of exposure and a "late" effect at about 24 hours. Brizzee and associates,[4] in a study of monkeys, found that destruction of the area postrema prevented early vomiting with exposure to 1200 r's, but that destruction of the dorsal sensory vagal

nucleus without injury to the area postrema was ineffective in controlling emesis; supradiaphragmatic vagotomy was also effective in preventing vomiting. Later work by these investigators indicated that the area postrema, and not simply the C-T zone, was the central emetic site for roentgen-ray irradiation in dogs as well.[4]

Because there is no definite evidence of neural fibers arising in the area postrema and passing to the vomiting center, it is suggested that the transmission of impulses from the area postrema to the vomiting center may occur by a neurohumoral mechanism.[4]

Recent studies by Isaacs[6] deal with vomiting induced by apomorphine in man with a maximum stimulating dose of 1 mg. subcutaneously; about one half of the subjects vomited after this injection. Body position altered the response to apomorphine. After individual subjects had been studied in various positions, it was concluded that recumbency of the trunk protected against the emetic effect, whereas the position of the head had no influence on the response. It was speculated that apomorphine may cause vomiting by sensitizing the central emetic mechanisms to afferent impulses from the vestibules, the neck, and other structures.

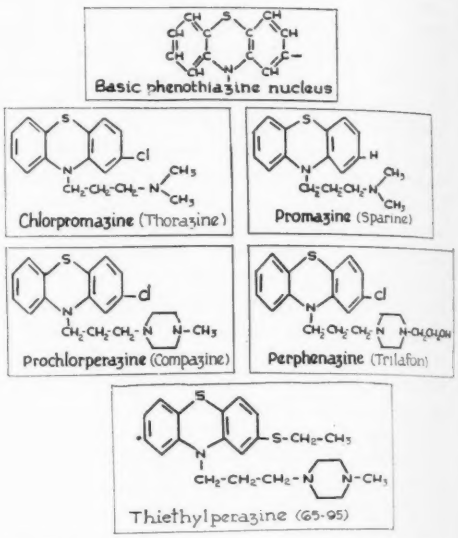
Studies on the Incidence and Control of Vomiting

Nausea and vomiting have been disturbing problems in such situations as pregnancy, operative intervention, uremia, cancer therapy and migraine. Intensive evaluations of drugs for clinical antiemetic activity began around the middle of the present century. Of the many agents studied to date, those of the phenothiazine group have been found most useful.

The basic phenothiazine nucleus consists of two benzene rings united through sulfur and nitrogen linkages. The various derivatives have been compounded by alteration of the side chains attached to the nitrogen link or to the carbon atom of the second benzene ring. The chemical structures of chlorpromazine, promazine, prochlorperazine, and perphenazine are illustrated in figure 2.

Before the availability of phenothiazines, Schmidt and associates[7] found dimenhydrinate (Dramamine) and diphenhydramine (Benadryl) to be essentially ineffective in preventing emetic response to apomorphine in cats

FIG. 2



Chemical structures of phenothiazine nucleus and derivatives.

and dogs. Others studied the effects of chlorpromazine on apomorphine-induced emesis in dogs by a dose of 0.05 mg. apomorphine per kilogram of body weight. Chlorpromazine, 2 mg. per kilogram, significantly depressed the incidence and frequency of vomiting and retching, and 10 mg. per kilogram completely prevented vomiting. Still other studies verified these findings in the dog, but found no protection against vomiting induced by copper sulfate (either orally or intravenously), lanatoside-C or veratrum alkaloids. With this pattern, they suggested that chlorpromazine acted by selective, but total, depression of the chemoreceptor-trigger zone. In cats, however, emesis induced by apomorphine, lanatoside-C, and copper sulfate (intravenously) was not prevented by chlorpromazine. These investigators concluded that there may be various types of chemoreceptors in the C-T zone and that chlorpromazine may block a portion of them.

Subsequently, many phenothiazine analogues have been evaluated and found to have variable antiemetic potencies. Rosenkilde and Govier[8] studied five phenothiazine agents in which emesis was induced by apomorphine in dogs. Mepazine and promazine were found to be ineffective, whereas perphenazine, prochlorperazine and chlorpromazine proved to be potent antiemetic agents in this situ-

ation. Wang[9] obtained similar results in dogs with both perphenazine and chlorpromazine except for the increased potency of perphenazine in suppressing the emesis associated with administration of morphine sulfate, lanatoside-C, and Hydergine.

Clinical evaluations of the antiemetics were performed as soon as animal studies seemed to preclude serious adverse reactions. Some found that chlorpromazine was effective in suppressing nausea and vomiting induced in a great number of clinical situations [including labrynthitis, uremia and reactions to disulfiram (Antabuse), morphine, nitrogen mustard, and protoveratrine]. Dickinson,[10] in a preliminary report, indicated that perphenazine seemed to be effective against vomiting caused by roentgen-ray irradiation.

In postoperative patients Knapp and Beecher[11] used placebos, chlorpromazine, dimenhydrinate, and various doses of pentobarbital. They observed their patients carefully for retching and vomiting for 24 hours postoperatively and analyzed the results in two groups: all retching, nausea and vomiting (1) in the first 4 hour postoperative period and (2) in the total 24 hour postoperative period. The results of this study are demonstrated in table 2. In a series of patients who had undergone major gynecologic operations, Dodge, Schotz and Corbit[12] administered either a placebo solution or 50 mg. of chlorpromazine intravenously in 2,000 ml. of solution over a 24 hour period. The anesthetic agents were not indicated. Nausea and vomiting in this 24 hour period were observed in 78% of the control subjects and in 63% of the treated patients. The incidence of vomiting in the group on placebos in the studies of Moore and associates[13] was 18%, whereas in a similar, but group treated with perphenazine, the incidence was 6 per cent.

Other workers who had not used phenothiazine agents had reported equivocal or ineffective results with agents considered to have antiemetic properties. Dent and associates,[14] in 1955, in an evaluation of cyclizine (Marezine), recorded the incidence of postoperative vomiting. In the control series of 2,000 patients, 27% of the patients had vomiting, as compared to 21% in the group of 1,000 who received cyclizine. Moore and co-

TABLE 2

INCIDENCE OF POSTOPERATIVE NAUSEA, RETCHING AND VOMITING IN CONTROL SUBJECTS AND SUBJECTS RECEIVING VARIOUS ANTIEMETIC DRUGS

Agent Used	*Total No. Patients*	*Vomiting*		*Nausea and Retching*		*Vomiting, Nausea and Retching*	
		Incidence Per Cent	*Reduction Per Cent*	*Incidence Per Cent*	*Reduction Per Cent*	*Incidence Per Cent*	*Reduction Per Cent*
Thiethylperazine a*	46	13	61	35	32	35	32
b*	30	17	51	37	28	37	28
c*	160	11	67	23	57	23	57
d*	256	12	65	29	44	29	44
control	190	34		51		51	
Thorazine[11]	152					34	41
Dramamine	85					61	
Pentobarbital							
100 mg.	67					62	
150 mg.	85					43	26
control	165					58	
Thorazine[12]	51					63	19
control	52					78	
Perphenazine[13]	304	6	65				
control	306	18					
Marezine[14]	1000	21	24				
control	2000	27					
Dramamine[12]	8849	13	43				
control	1502	23					
Marezine[15]	1060	22				36	5
Bonamine	606	28				41	
control	657					37	

a*—10 mg. suppositories preoperatively
b*—5 mg. I. M. immediately postoperatively
c*—10-15 mg. I. M. immediately postoperatively
d*—composite of a, b and c series

workers[13] observed vomiting in 23% of 1,502 control patients and in 13% of 8,849 patients treated with dimenhydrinate. Tillman and co-workers[15] detected no beneficial effect with meclizine (Bonine) or cyclizine in the control of postoperative vomiting; vomiting occurred in 23% of their control subjects and in 27% of the patients who received meclizine, and in 22% of the patients who had cyclizine.

Nausea and vomiting are frequent and unpleasant responses to administration of nitrogen mustard, the reactions usually beginning 20 to 30 minutes after therapy and subsiding within a few hours. These reactions occur with all therapeutic doses, although the larger a single dose, the earlier is vomiting initiated. The incidence of this complication has been variously recorded as 86% (nausea and vomiting),[16] 63% (nausea) and 18% (vomiting),[17] 57% (nausea with or without vomiting),[18] and 51% (nausea with or without vomiting).[19] Moyer and associates[20] gave chlorpromazine to patients who had received nitrogen mustard; 40% of these patients had nausea or vomiting or both during therapy. In each of these series, nausea or vomiting occurred at some time during the individual course of therapy, which usually implied a minimum of 4 consecutive days of 0.1 mg. per kilogram of nitrogen mustard intravenously on each occasion. No series recorded the incidence for each day of therapy.

Clinical Study of Thiethylperazine*

Our present studies are undertaken to evaluate the effectiveness of a new phenothiazine agent, thiethylperazine, in selected clinical states. This drug differs from other phenothiazines in that it has a thioethyl group at the carbon bond of the second benzene nucleus. This agent has been demonstrated in animal work to have low toxicity potential as related to the effective dose.** As an adrenolytic agent, it has proved to be 7 times more potent than dihydroergotamine. Conversely, its ability to act as an anticholinergic was 900 times weaker than atropine. Potentiation of barbiturate narcosis has been minimal. Antiemetic activity has been demonstrated in the presence of both intravenous apomorphine and intragastric copper sulfate, with an effective dosage range of 0.2 to 0.8 mg. per kilogram when given intravenously to dogs. The initial clinical studies suggested antiemetic activity in nausea and vomiting of pregnancy, uremia, and metastatic carcinoma. Even with extremely large doses the beneficial effect on psychiatric problems is slight. The evidence of adverse reactions to date has been limited to extrapyramidal symptoms, drowsiness, "dry nose," "dry mouth," and occasionally increased anxiety. These side-effects occurred usually when 30 mg. or more were given for more than 2 or 3 days consecutively. No hepatic, hematopoietic, or renal toxicity has been recorded (Table 3).

*Torecan (thiethylperazine) supplied by Sandoz, Inc.
**Personal communication, Sandoz, Inc.

Antiemetic Activity of Thiethylperazine in Postoperative Patients

All operative procedures which required anesthesia except those confined strictly to local blocks (but not excluding spinal anesthesia) were included in this consecutive series. No attempt was made to select the patients according to the anesthetic agents, anesthesiologist, or type of procedure. Observations were limited only to patients of the surgeons who cooperated in the study. Observations were made by the attending nursing personnel in the postoperative recovery room. The nursing attendants were aware that the patients were being observed for nausea, vomiting and changes in blood pressure, but not of the specific nature of the study or of changes in the regimen in order to avoid bias in the observations. Nausea was recorded if the patient complained of the symptom or exhibited vomiting activity but did not actually have emesis of gastric con-

TABLE 3

CLINICAL CASES TREATED FOR VOMITING

Diagnosis	*Observations*	*Relief of Vomiting*	
		Complete	*Partial*
Inflammatory states			
Hiatal hernia	5	3	2
Chronic gastritis	4	3	1
Acute gastroenteritis	17	14	3
Peptic ulcer	5	5	0
Biliary disease with acute colic	5	5	0
Acute appendicitis	3	3	0
	39	33	6
Noninflammatory states			
Uremia	1	1	0
Migraine: acute therapy only	5	4	1
Migraine: chronic therapy	5	3	2
Situational, psychophysiologic or functional vomiting	39	35	4
	50	43	7

tents. The patients were held under close observation until fully awake and free of nausea; this period varied from 2 to 6 hours postoperatively. These factors were similar in both the control and the thiethylperazine treated series.

A control group of 190 patients, who received no thiethylperazine, was observed in which the preoperative and postoperative medications were ordered by the attending surgeon and may or may not have included antiemetic drugs.

In the treated patients, no antiemetic agent was used other than thiethylperazine. In 46 patients, this drug was given in a single dose, as a 10 mg. suppository, just as the patient entered the operating room. Subsequently, another 30 patients received 5 mg. intramuscularly at the time of transfer to the recovery room. One hundred-sixty patients were given 10 to 15 mg. of thiethylperazine intramuscularly upon returning to the recovery room.

In the control series, 96 patients (51%) had nausea or retching or both and 64 (34%) had vomiting (Table 2).

When 10 mg. suppositories of thiethylperazine were used, the incidence of vomiting declined to 13% of the patients, whereas that of nausea and vomiting fell to 35 per cent. Comparison of these figures with those of the control series reveals a reduction in incidence of vomiting by 61% and of nausea and vomiting by 32% respectively. With reduction of the dose to 5 mg. and with intramuscular administration, vomiting was recorded in 17% of the patients, whereas nausea and vomiting together were noted in 37% (a reduction of 51% and 28% respectively).

On the basis of these figures, a dosage of 10 to 15 mg. intramuscularly was selected. With this regimen, vomiting occurred in 11% of the patients (reduction of 67%) and nausea and vomiting in 23% (reduction of 57%).

Among the total of 236 patients observed, the incidence of vomiting was 13% and of nausea and vomiting 27 per cent. These figures represent a decrease of vomiting by 62% and of nausea and vomiting by 47% from the values for the control series.

Results of this series can be compared with those of previous studies, as demonstrated in table 2. The least reduction in postoperative nausea and vomiting was noted in the series involving use of cyclizine, dimenhydrinate, and pentobarbital. In the perphenazine series, vomiting was reduced by 65%, whereas with chlorpromazine, nausea and vomiting decreased by 41 per cent.

Currently, observations with use of the 10 to 15 mg. intramuscular injection of thiethylperazine are being continued as the drug possesses greater antiemetic potentialities than that of other phenothiazine agents.

Antiemetic Activity in Clinical Conditions Associated with Vomiting

The states in this study have been arranged in two clinical groups. In the first group of these patients nausea and vomiting were associated with an inflammatory reaction, and in the second group, these symptoms occurred in the absence of any inflammatory process, as demonstrated in table 3.

In the patients with associated inflammatory states, many cases represented acute disturbances and intramuscular injections of 10 to 20 mg. were found to yield more prompt and more satisfactory results. Relief occurred in these patients within an interval varying from 30 to 50 minutes after administration of thiethylperazine. Administration of 10 mg. of the drug orally or by suppository was usually effective in maintaining relief. Among a total of 39 patients in this group, 33 obtained complete relief and 6 partial relief. The dosage of thiethylperazine was increased in the 6 patients who received only partial relief initially; 3 of these had complete relief of nausea and vomiting.

The importance of psychologic factors in many patients in the second group (the noninflammatory cases) suggests need for further study of the site and mode of action of this drug. Four of these patients experienced vomiting episodes under certain conditions or situations, but the episodes were aborted by the optimal dose of 10 mg. three times a day, administered two days before the precipitating event and administration of a 10 mg. suppository one hour before. The 5 patients with migraine were selected because of the presence of well-established aura in each and because nausea and vomiting had been a consistent part of their migraine episodes. Four distinct series of observations were carried out on these patients with the idea of establishing an optimal mode of management. In no instance did thiethylperazine abort the headache, but it

was effective in relieving the nausea and vomiting. When the suppository was used in conjunction with Cafergot (a caffeine and ergotamine combination) at the onset of the aura, the headache and the nausea and vomiting were prevented; this result suggests the value of thiethylperazine as an adjunct in the management of the migraine state. The terms "psychophysiologic gastrointestinal reactions" and "functional gastrointestinal disturbances" have been used to indicate predominance of psychic disturbances and gastrointestinal disturbances, respectively. Optimal dosage in these groups of patients varied greatly and the total of 50 observations in the second group required careful individualization. When all methods of administration were considered, 43 received complete relief and the others only partial relief. Six of the patients in the second group had been taking another phenothiazine medication previously; the change to thiethylperazine resulted in more specific antiemetic action, although the tranquilizing action was not as great, and additional sedation was necessary at irregular intervals.

During the course of these 89 observations, 7 patients had adverse side-effects. One patient developed a gastric ulcer. Another patient experienced hypotension when the thiethylperazine was given in combination with dihydroergotamine. The remaining 5 patients had minor symptoms of "dry nose," "dry mouth," "lightheadedness," or disturbed gait. This represents an incidence of side-effects of 8% in this group of patients. In every instance the symptoms disappeared after the drug was discontinued.

Antiemetic Activity with Nitrogen Mustard ("Triple Treatment") Therapy

A third part of the present study consisted in observations on a group of patients with carcinoma who received nitrogen mustard.

The first small group of 12 patients received antiemetic treatment before administration of nitrogen mustard by the attending physician, in doses of 0.1 to 0.2 mg. per kilogram. They were then observed for the onset of retching or vomiting. When either was observed, a 10 mg. suppository of thiethylperazine was administered. Nausea and vomiting occurred in 7 of these 12 patients within 45 minutes to 3 hours after administration of nitrogen mustard therapy. No immediate suppressive effect on emesis was demonstrable with this regimen.

It was then decided to increase the dose of thiethylperazine to 20 mg. and to administer it before antitumor therapy. At this time, 2 patients who received "triple therapy" (oxygen, nitrogen mustard, and roentgen-ray irradiation in combination) in divided doses were observed. In addition, 4 patients who received nitrogen mustard alone were included in the group. In all but 6 of these 76 patients, thiethylperazine was the sole antiemetic pretreatment agent, given 15 to 60 minutes before specific cancer therapy. Vomiting occurred in 41 of these 76 patients (53%) as compared to the previous 7 of the 12 (58.3%) in the post-treatment group. Vomiting occurred in 15 of 25 patients who received 10 mg. of thiethylperazine before cancer therapy.

No definite conclusions can be drawn from results recorded to date. Two patients who had received previous courses of "triple treatment" with pretreatment administration of other antiemetic agents volunteered expressions of less discomfort and less vomiting during the therapy. Because of the inconclusiveness of the present data and the subjective improvement in some patients who received thiethylperazine, an evaluation of increasing doses of the parenteral preparation is needed to permit comparison of the two regimens.

Conclusions

Thiethylperazine, when administered to postoperative patients and particularly in optimal dosage of 10 to 15 mg. intramuscularly, notably suppressed the incidence of nausea and vomiting. Thiethylperazine was found to be an extremely effective antiemetic in a large number of clinical conditions attended by vomiting. The optimal dosage is variable and must be individualized. Single and repeated administrations have been satisfactory and safe in doses described. To date results with this drug in patients with nitrogen mustard-induced vomiting have only suggested possible suppression of the severity of nausea and vomiting. The variability of the dosage used, according to the particular stimulus, may explain the equivocal results in the face of such a potent emetic agent as nitrogen mustard.

The corollary problem of each new effective drug resides in possible adverse responses. To date the major complication of renal, hepatic

and hematopoietic toxicity has not been encountered with administration of thiethylperazine as described in this report. Daily administration of 30 mg. or more of thiethylperazine precipitated complaints of disturbed gait, "dry mouth," "dry nose," and "lightheadedness" in a small number of patients. However, in no patient did these symptoms persist after withdrawal of the drug for a 24 hour period. Hypotension was observed in only one patient who received an injection of dihydroergotamine after administration of a 10 mg. suppository of thiethylperazine. Again, recovery was spontaneous and prompt. The occurrence of a gastric ulcer during chronic administration of thiethylperazine in one patient on the 30 mg. daily program was disturbing, but could not be unequivocally related to this drug. No cutaneous eruptions have been observed.

On the basis of results in a large number of patients in a widely variable setting of clinical situations, it is believed that thiethylperazine constitutes a new, safe, and potent antiemetic phenothiazine.

Acknowledgments

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References

1. Amols, W., and Merritt, H. H.: Vomiting: Neural Mechanisms and Control by Chlorpromazine, Neurology 5:645, 1955.
2. Luskiewicz, A.: Vomiting and Eructation with Regard to the Upper Respiratory Organs, Acta oto-laryng. 46:27, 1956.
3. Borison, H. L., and Wang, S. C.: Physiology and Pharmacology of Vomiting, Pharmacol. Rev. 5:193, 1953.
4. Brizzee, K. R., Calton, F. M., and Vitale, D. E.: Effects of Selective Placement of Lesions in Lower Brain Stem Structures on X-irradiation Emesis in the Dog, Anat. Rec. 130:533, 1958.
5. Borison, H. L., Brand, E. D., and Okrand, R. K.: Emetic Action of Nitrogen Mustard (mechloretheamine HCl) in Dogs and Cats, Am. J. Physiol. 192:410, 1958.
6. Isaacs, B.: The Influence of Head and Body Position in the Emetic Action of Apomorphine in Man, Clin. Sc. 16:215, 1957.
7. Schmidt, C. C., Sata, E., Brizzee, K. R., and Borison, H. L.: Effects of Dramamine and Benadryl on Apomorphine-induced Emesis in Dogs and Cats, Proc. Soc. Exper. Biol. & Med. 82:441, 1953.
8. Rosenkilde, G., and Govier, W. M.: A Comparison of Some Phenothiazine Derivatives in Inhibiting Apomorphine-induced Emesis, J. Pharmacol. & Exper. Therap. 120:375, 1957.
9. Wang, S. C.: Perphenazine, a Potent and Effective Antiemetic, J. Pharmacol. & Exper. Therap. 123:306, 1958.
10. Dickinson, R. J.: Preliminary Report on Trilafon in Radiation Sickness, Radiology 70:259, 1958.
11. Knapp, M. R., and Beecher, H. K.: Postanesthetic Nausea, Vomiting and Retching: Evaluation of the Antiemetic Drug Dimenhydrinate (Dramamine), Chlorpromazine, and Pentobarbital Sodium, J.A.M.A. 160:376, 1956.
12. Dodge, H. C., Schotz, S., and Corbit, J. D.: Chlorpromazine Intravenously in Postanesthetic Nausea and Vomiting, Obst. & Gynec. 9:184, 1957.
13. Moore, D. C., Bridenbaugh, L. D., Van Ackeren, E. G., and Cole, F. V.: Control of Postoperative Vomiting with Perphenazine (Trilafon): A Double Blind Study, Anesthesiology 19:72, 1958.
14. Dent, S. J., Ramashandra, V., and Stephen, C. R.: Postoperative Vomiting: Incidence, Analysis and Therapeutic Measures in 3000 Patients, Anesthesiology 16:564, 1955.
15. Tillman, W. W., Wise, G. T., and Crawford, O. B.: Evaluation of Marezine and Bonamine in Lowering the Incidence of Postoperative Nausea and Vomiting, Anesthesiology 17:112, 1956.
16. Zanes, R. P., Doan, C. A., and Hoster, H. A.: Studies in Hodgkins Disease, J. Lab. & Clin. Med. 33:1002, 1948.
17. Koyama, Y., and Tokuyama, H.: Clinical Experience with Nitromin, Ann. New York Acad. Sc. 68:1105, 1958.
18. Lynch, J. P., Ware, P. T., and Gainsler, A.: Nitrogen Mustard in the Treatment of Inoperable Bronchogenic Carcinoma, Surgery 27:368, 1950.
19. Hatch, H. B., Bradford, J. D., and Ochsner, A.: Nitrogen Mustard in the Treatment of Advanced Carcinoma of Lung: Analysis of 198 Cases, J.A.M.A. 160:1129, 1956.
20. Moyer, J. H., Kinross-Wright, V., and Finney, R. M.: Chlorpromazine as a Therapeutic Agent in Clinical Medicine, A.M.A. Arch. Int. Med. 95:202, 1955.

Epidemiology of Poliomyelitis in Arkansas — 1959*

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Immunization of certain segments of the population with Salk vaccine has been reflected in an altered pattern of distribution of the disease.

POLIOMYELITIS WAS ON THE INCREASE throughout the country in 1959. Arkansas was no exception, the 317 cases representing the highest incidence since 1954. The epidemic in Little Rock and surrounding Pulaski County was the first southern outbreak since the Salk vaccine came into widespread use. A review of past epidemiologic characteristics in this southern state will supplement a detailed analysis of the changing epidemic pattern observed in 1959.

Materials and Methods

Epidemiologic information on each case in 1959 and for all previous years was obtained from the Arkansas State Health Department, Division of Communicable Disease Control. In 1959, each case reported as paralytic had a 60 day follow-up to determine the severity of residual paralysis. This follow-up was performed by physiotherapists whenever possible, but many of the examinations were done by private physicians or county health nurses. All reported cases of poliomyelitis in 1959 were included, as well as the 10 reported cases of aseptic meningitis. There appeared to be a high degree of validity of the diagnoses since all but 16 patients either had pleocytosis in the spinal fluid of greater than 10 cells per cu. mm., an enterovirus isolated from their stool specimen, a diagnostic change in poliovirus complement-fixing antibody titer, or evidence of residual paralysis at the end of 60 days. Vaccination status in each case included all injections received prior to two weeks before onset. Age at the last birthday determined the age classification of each case.

Since there has been little change in the total state population in the past 20 years, the 1950 census figures were used in calculating all attack rates, both state-wide and most rates for Pulaski County. For 1959, the estimate for Pulaski County by the Arkansas Industrial Research Center was used. Resident birth information since 1950 for the age groups under 10 and an age projection from the 1950 U. S. Census for ages 10 and over formed the basis for age distribution of the population in Pulaski County in 1959.

The Pulaski County Chapter of the National Foundation March of Dimes conducted a survey of polio immunization on August 16 and 17 in conjunction with an emergency fund raising campaign. The county was surveyed by elementary school districts and as a result, a 35% sampling of the population was obtained.

Etiologic specimens consisting of stools and acute and convalescent sera were mailed unrefrigerated to the Kansas City Field Station by the local physician, hospital, or county health nurse. Virtually all specimens were sent to the Kansas City Field Station. All stools were processed by passage in monolayer monkey kidney tissue culture. Acute and convalescent sera on the patients without an enterovirus isolation had complement fixation tests performed against the three types of poliovirus by a standard method. Details of the laboratory procedures may be found elsewhere.[1-5]

Demography

Arkansas is a representative southern state, predominantly rural but making ever-increasing strides towards industrialization. It is a

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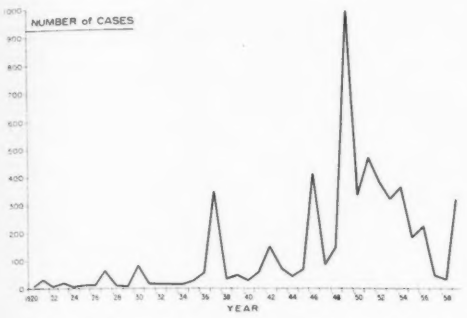
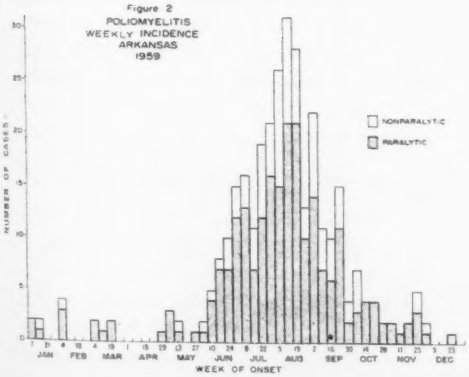
Figure 1
ANNUAL INCIDENCE OF POLIOMYELITIS, ARKANSAS, 1920-1959



major producer of cotton and oil and is rich in mineral resources, supplying 98% of the Nation's bauxite.

Little Rock, the capitol of Arkansas, is located in Pulaski County and is the only standard metropolitan area in the state. Since 1940, when the state population was 1,949,387, there has been an emigration from the state resulting in a population of 1,909,511 in 1950 and an estimated 1,786,787 in 1958. Despite this over-all decrease in population there has been a strong rural-urban movement within the state, with the farm population decreasing 35% since 1950 and urban areas increasing. The Pulaski County population has increased by an estimated 35% since 1950. The proportion of Negroes in the state population has been stable, being 25.8% in 1930 and 22.4% in 1950. The proportion of Negroes in rural and urban communities has remained approximately the same, there being no concentration of Negroes in urban centers, as is the case in many northern communities.

Figure 2
POLIOMYELITIS
WEEKLY INCIDENCE
ARKANSAS
1959



Epidemiology—State-Wide

Prior to the 1930's epidemic poliomyelitis was confined to the northern part of the United States. Arkansas' first outbreak was in 1937 with 344 reported cases (Fig. 1). The next year of high incidence was 1946, and from 1949 to 1954 the annual incidence exceeded 300 cases with an all-time peak of 992 cases in 1949. Beginning in 1955 there was a sharp decline, the 1958 incidence of 33 cases being the lowest since 1935. In 1959 there were 317 cases, 226 paralytic and 91 nonparalytic (Fig. 2). The several cases reported during the winter months were not unusual for this southern state. There was a sharp rise in June which continued into July and August, with the peak of 31 cases (including the midseasonal case) occurring in the week ending August 12.

Prior to 1956, only 6 to 14% of the poliomyelitis cases were Negroes (Table 1). Beginning abruptly in 1956, an increasing proportion of the poliomyelitis cases had been Negroes. Thirty-five per cent of the cases in 1959 were Negroes. The proportion of Negroes in the general population has remained constant through the years, accounting for about one fourth of the total.

The highest incidence of poliomyelitis in this state previously was in the 0 to 4 age group. An over-all trend toward an increasing rate in the 5 to 9 age group had not appeared. However, the 0 to 4 and 5 to 9 rates in whites in 1952 and 1954 were comparable (Table 2). There had not been any indication of increasing incidence in the 10 to 14 age group. The

TABLE 1

NUMBER AND PERCENTAGE OF CASES OF POLIOMYELITIS IN NEGROES IN ARKANSAS, 1944-1959

Year	*Total Cases*	*Negro Cases*	*% Cases Negro*
1944	44	6	13.6
1945	69	8	11.6
1946	408	36	8.8
1947	83	5	6.0
1948	146	12	8.2
1949	992	104	9.6
1950	337	34	10.4
1951	466	60	12.9
1952	383	53	13.8
1953	322	42	13.0
1954	365	44	12.0
1955	186	19	10.2
1956	222	55	24.8
1957	50	14	28.0
1958	33	8	24.2
1959	317	111	35.0

TABLE 2

AGE SPECIFIC ATTACK RATES OF POLIOMYELITIS FOR YEARS OF HIGH INCIDENCE* AMONG WHITES, AGES 0 TO 14, ARKANSAS

Year	Cases by Age Group			Annual Rates/100,000 Population by Age Group		
	0-4	5-9	10-14	0-4	5-9	10-14
1937	Not Available				Not Available	
1946	168	98	46	99.0	64.0	33.8
1949	450	248	98	265.3	162.0	72.0
1950	125	65	43	73.7	42.4	31.6
1951	185	95	49	109.1	62.0	36.0
1952	113	91	61	66.2	59.4	44.8
1953	110	66	45	64.8	43.1	33.1
1954	107	99	37	63.1	64.7	27.2
1959	87	49	21	51.3	32.0	15.4

*Includes years with more than 300 cases

5 to 9 paralytic rate in whites also approximated the 0 to 4 rate in 1954, suggesting a trend toward an increasing age incidence (Table 3).

In 1959, the 0 to 4 age group had by far the highest incidence. The 0 to 4 incidence in whites was 1.6 and 2.2 times that in the 5 to 9 for total and paralytic cases, respectively. The 3.7 per 100,000 paralytic rate in the 10 to 14 year old white population was exceedingly low (Table 3). The 0 to 4 negro rate in 1959 was 2.8 and 3.1 times that in the 5 to 9 for total and paralytic cases, respectively. In previous years a greater proportion of cases in Negro than white had been under five. In 1959, 65.8% of the negro cases and 42.2% of the white cases were under five.

Only 38 of the 226 paralytic cases (16.8%) had received 3 or more injections of Salk vaccine. Seven of these had received 4 injections. A 60 day follow-up examination determined the severity of residual paralysis in 225 of the 226 paralytic cases (Table 4). A summary of these examinations by vaccination status revealed that 8 of the 38 triply vaccinated paralytic cases had no residual paralysis. Salk vaccination appeared to moderate the severity of residual involvement when the proportion of cases with severe disability or death are compared by vaccination status. Only 16% (6 of 38) of the triply vaccinated compared to 42% (56 of 158) of the unvaccinated had severe disability or had died at the time of the 60 day follow-up (chi square = 5.48, p = less than 0.02). One of the 10 deaths was in a triply vaccinated 4 year old white girl who had received her third injection over two years before onset.

Epidemiology—Pulaski County

The 73 cases, 55 paralytic and 18 non-paralytic, in Pulaski County produced an attack rate of 27.4 per 100,000 population. Previous outbreaks with attack rates greater than 25 per 100,000 occurred in Pulaski County in 1937, 1946, 1949, and 1951. The incidence rate for Little Rock and Pulaski County had regularly exceeded that of the rest of the state except in 1949 when there was a large rural outbreak in northeast Arkansas. In 1959 the epidemic extended from mid-June to early September, reaching a peak of 10 cases in the week ending July 22. The racial incidence in Pulaski County for the epidemics of 1946, 1949, 1951, and 1959 were compared (Fig. 3). Even in the most severe epidemic in the county's history in 1951, with an over-all attack rate of 67.6 for 100,000,

TABLE 3

AGE SPECIFIC ATTACK RATES OF PARALYTIC POLIOMYELITIS AMONG WHITES BY AGE GROUPS, 1953, 1954, AND 1959,* ARKANSAS

Year	Cases by Age Group			Annual Rates/100,000 Population by Age Group		
	0-4	5-9	10-14	0-4	5-9	10-14
1953	77	34	23	45.4	22.2	16.9
1954	85	62	23	50.1	40.5	16.9
1959	74	31	5	43.6	20.2	3.7

*Paralytic status of cases not available prior to 1953

TABLE 4

60 DAY RESIDUAL INVOLVEMENT OF PARALYTIC POLIOMYELITIS* BY STATUS OF VACCINATION, ARKANSAS—1959

Residual Involvement	*Vaccination Status***		
	0	*1-2*	*3 or more*
No residual	19	4	8
Minor paralysis	32	9	8
Significant paralysis	51	5	16
Severe paralysis	48	10	5
Death	8	1	1
Total	158	29	38

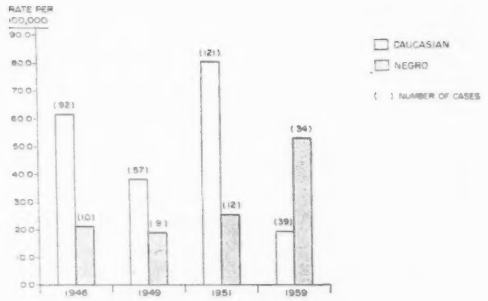
*Includes 225 of the 226 paralytic cases.
**Excludes injections of Salk vaccine within 2 weeks of onset of illness.

there were only 12 negro cases. Prior to 1959 the negro rate was one half to one third that of the white population. In 1959, with 34 of the 73 cases in Negroes, the negro attack rate was almost 3 times that of the white population (53.2 per 100,000 compared to 19.3 per 100,000). The negro paralytic attack rate in Negroes was one fourth that of the white population in 1951 and 4 times that of the white population in 1959. There has been no appreciable change in the 1:3 ratio of Negroes to whites in the population of Pulaski County in the past 30 years.

In the past Pulaski County epidemics the age specific rate in the 0 to 4 age group had been above that in the 5 to 9 age group, but there had not been more than a 1.6-fold difference. In 1959 the 0 to 4 rate was twice that of the 5 to 9 for the white population, and almost 4 times that of the 5 to 9 in the negro population. Thus there was a relative increase in the preschool age incidence.

Only 7 of the 55 paralytic cases (13%) in Pulaski County had received 3 or more injections of Salk vaccine. None of the 4 who died had received 3 injections. Results of the vaccination survey conducted in mid-August, 1959, by the Pulaski County Chapter of the National Foundation, showed that over three fourths of the white population in every 5 year age group below 20 had received 3 or more injections of vaccine (Fig. 4). The negro population was less well vaccinated with only 40% under 5 years and less than 60% in each 5 year age group from 5 to 19 having received 3 injections. Protection by the Salk vaccine is suggested since only 3 of the 31 negro paralytic patients and 4 of the 24 white paralytic patients were triply vaccinated.

Figure 3 POLIOMYELITIS INCIDENCE, BY RACE EPIDEMIC YEARS 1946, '49, '51, and '59 PULASKI COUNTY, ARKANSAS



Etiologic Studies

A poliomyelitis etiologic study program, organized in cooperation with the Arkansas Health Department, encouraged physicians and public health nurses to send stool samples and paired sera on all the cases throughout the state to the Kansas City Field Station for virus testing. The specimens were sent unrefrigerated. Stool specimens were tested in monkey tissue culture. If the fecal sample failed to yield an enterovirus, the available paired sera were tested for poliovirus complement-fixing antibodies by a standard method. A fourfold or greater rise or fall in complement-fixing antibodies was the serologic criterion for diagnosis.

Eighty-eight per cent of the patients had specimens submitted. This included a stool sample on all but 16 patients who had paired sera alone. The paired sera from 7 of these 16 were anticomplementary and were excluded from analysis. Thus an attempt was made to identify the etiologic agent in 272 cases, 194

Figure 4 PERCENTAGE OF PERSONS 0-19 YEARS, BY RACE WITH 3 OR MORE SALK INJECTIONS PULASKI COUNTY, ARKANSAS AUGUST 1959*

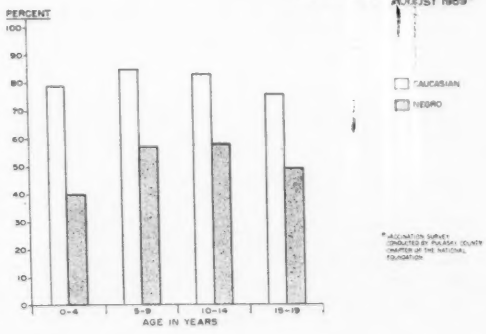


TABLE 5

PROVEN ENTEROVIRUS INFECTIONS, ARKANSAS—1959

Clinical Status	Total Cases	Proven Infections				Per Cent Proven Infections
		Polio 1	Polio 2	Polio 3	Other Enteroviruses	
Paralytic	194	138	2	2	8	77.3
Nonparalytic	78	25	2	0	8	44.9
Total	272	163	4	2	16	68.0

paralytic and 78 nonparalytic patients (Table 5). The etiology was established for 185 (68%). Enterovirus infection was confirmed in 77.3% of the paralytic cases and 44.9% of the nonparalytic cases. All but 29 of the proven cases were by virus isolation. While 95% of the proven paralytic cases were due to poliovirus (overwhelmingly type 1), 23% of the proven nonparalytic patients were associated with a nonpoliovirus infection. Thus a significant number of the nonparalytic cases were related to nonpoliovirus infection. The nonpolioviruses isolated from 5 patients have been identified. Strains of Coxsackie B-5 and ECHO type 6 came from two paralytic patients, and one strain of Coxsackie B-5 and two strains of Coxsackie B-2 were isolated from 3 nonparalytic patients. The nonpoliovirus isolations were not confined to any particular geographic sector of the state, only 2 such isolations being made from Pulaski County cases.

Discussion

The epidemics in Chicago in 1956,[6] Washington, D. C., in 1957,[7] Detroit in 1958,[8] and more recently in Des Moines[9] and Kansas City[10] during 1959 have documented the striking change in the epidemic pattern of poliomyelitis in the northern part of the country since the introduction of the Salk vaccine. There can be little doubt that the Salk vaccine has played a major role in producing the new pattern. Since there have always been certain differences in the epidemiologic characteristics of poliomyelitis as observed in the northern and southern part of the United States, it is important to consider separately the effect of the Salk vaccine on the previously established epidemic pattern in the south. The increased incidence in Arkansas and especially the epidemic in Little Rock in 1959 afforded this opportunity.

Prior to 1956, only six poliomyelitis outbreaks could be found in the United States where the incidence in Negroes was greater than in whites[11-15] (Table 6). In none did the negro rate exceed the white rate by as much as twofold. The negro incidence was significantly greater than that of the white population only in the severe 1939 Charleston, S. C., epidemic and in the smaller outbreak in Birmingham, Alabama, in 1952. Before 1956, national figures showed the white rate to be usually 2 to 3 times that of the Negroes. In the major poliomyelitis outbreaks since 1955 the negro rate exceeded the white rate by 6 to 20-fold. In 1956 this same trend began abruptly in Arkansas, coinciding with the year that the Salk vaccine came into widespread use. The incidence in Negroes in the 1959 Pulaski County epidemic was almost three times that of the white population. One possible explanation for this increased incidence is that the Negro is failing to obtain naturally acquired immunity early in life and at the same time is failing to take advantage of artificial means of immunization. Improved living standards and/or a restricted endemic circulation of poliovirus since 1954 may have contributed to this failure to acquire natural

TABLE 6

POLIOMYELITIS OUTBREAKS IN UNITED STATES WHERE NEGRO RATE EXCEEDED WHITE RATE PRIOR TO 1956

Year	Location	Population		Cases		Rate 100,000 Population	
		White	Negro	White	Negro	White	Negro
1916	Maryland[11]	1,149,200	239,500	285	68	24.8	28.4
1930	Chicago, Ill.[11]	3,089,300	227,800	173	18	5.6	7.9
1939	Charleston, S. C.[12,13]	49,700	61,800	73	107	146.9	173.1
1941	Atlanta, Ga.[15]	197,800	104,500	68	37	34.4	35.4
1952	Birmingham, Ala.[14]	387,100	46,700	48	10	12.4	21.4
1955	Cincinnati, Ohio[14]	705,900	101,100	48	9	6.8	8.9

immunity. On the other hand, the white population which has a relatively low level of naturally acquired immunity has participated more vigorously in Salk vaccination programs.

Accompanying the high negro rates in Chicago, Detroit, Des Moines, and Kansas City was a geographic concentration of cases due to the sharply demarcated negro and low socioeconomic community in each of these cities. There was no geographic concentration of cases in Little Rock, possibly because the Negro and low socioeconomic community is spread throughout the metropolitan area.

The greater concentration of cases under 5 years in southern states as compared with the distribution in the northern part of the country has been repeatedly emphasized. Three year olds had the largest percentage of cases from 1948 to 1952 in North Carolina, and from 1949 to 1951 in the white population of Virginia. Two year olds had the largest percentage of cases from 1948 to 1952 in the white population of Tennessee. One year olds had the largest percentage of cases in the white population of Alabama from 1948 to 1952.[16] The 0 to 4 age group had consistently experienced the highest attack rate in previous Arkansas and Pulaski County outbreaks. However, the rate for the 5 to 9 year group of the white population was comparable to the 0 to 4 rate in 1952 and 1954. The highest incidence in 1959 was clearly in the 0 to 4 age group for both the negro and white population. The relative increase in the attack rate of the 0 to 4 over the 5 to 9 age groups in Pulaski County was greater than seen in prior outbreaks. The shift of the highest age incidence from the 5 to 9 to the 0 to 4 age group in the major outbreaks in the northern part of the country since 1955 marked the return to so-called "infantile paralysis." At least two explanations may be offered for this alteration in age incidence. First, programs of Salk vaccination have been primarily geared to reach school age children with relatively little emphasis having been placed on vaccinating preschool age children. Surveys of vaccination in Little Rock and other cities throughout the United States demonstrated that the 5 to 14 age group was much better protected than the preschool age group, especially in the low socioeconomic groups. Second, because of the high levels of Salk vaccination in the middle and upper socioeconomic groups, most of the cases in the epidemics since 1955 have been from the low socioeconomic groups. This group usually had the largest proportion of cases in the 0 to 4 age group before the Salk vaccine, even in communities in the northern part of the country.[17]

There can be little doubt of the efficacy of the Salk vaccine in reducing paralytic disease in Arkansas in 1959. Only 16.8% of the paralytic cases were triply vaccinated. The apparent modification of the severity of residual paralysis among these triply vaccinated cases supports the results obtained by detailed follow-up of muscle testing of the paralytic cases in the 1956 outbreak in Chicago. The 60 day follow-ups in the 1959 Des Moines, Iowa, epidemic were performed by two physiatrists and a physical therapist. Here also vaccination appeared to alter the severity of residual paralysis.[9] The effectiveness of vaccine in Pulaski County was estimated using the vaccination status of the population by age group and race as of mid-August 1959. A 91.8% reduction in paralytic disease among the triply vaccinated was calculated. This was probably an overestimate since using the vaccination status of the population in mid-August rather than that at the beginning of the outbreak would necessarily bias the result in favor of the vaccine. The actual degree of protection was probably closer to that calculated for the Des Moines and Kansas City epidemics—80% and 76.8% respectively.[17]

Summary

The reported cases of poliomyelitis in Arkansas during 1959, and especially those in the Pulaski County epidemic, provided the basis for the study of the changing epidemiologic characteristics in a southern state since the introduction of the Salk vaccine. The highest incidence was in the negro population and the highest rate was in the 0 to 4 age group for both races. Over 70% of the cases were paralytic and extensive etiologic study confirmed that poliovirus type 1 was the etiologic agent for virtually all these cases. The effectiveness of the Salk vaccine was discussed together with the importance of its role in explaining the alteration in the epidemic pattern.

Acknowledgment

We are indebted to Mrs. Bernice K. Ginocchio, Mrs. Mary Norris, and Mrs. Janis Molock for their assistance

in compiling the data and in shipping the laboratory specimens. The technical assistance of Mrs. Evelyn Welton is also gratefully acknowledged.

References

1. Wenner, H. A., and Miller, C. A.: Comparison of Methods for Recovering Poliomyelitis Viruses from Human Sources, Proc. Soc. Exper. Biol. & Med. 86:11, 1954.
2. Gravelle, C. R., Chin, T. D. Y., Adams, I. C., and Wenner, H. A.: Observations on Infections with Enteroviruses in Missouri, 1956, Missouri Med. 56:641, 1959.
3. Fulton, F., and Dumbell, K. R.: The Serological Comparison of Strains of Influenza Virus, J. Gen. Microbiol. 3:97, 1949.
4. Morgan, P., Carter, J. S., and Wenner, H. A.: An Apparatus Employed in Plate Complement-Fixation Tests, J. Lab. & Clin. Med. 42:655, 1953.
5. Baumeister, J., and Miller, C. A.: The Preparation of Poliomyelitis Complement-Fixing Antigens from Infected Tissue Culture Fluids, J. Infect. Dis. 98:27, 1956.
6. Nathanson, N., Thrupp, L. D., Hall, W. J., Langmuir, A. D., Cornell, R. G., Forester, H. E., Church, R. E., Hall, J. B., Hildebrand, M., and Shaughnessy, Morrissey R.: Epidemic Poliomyelitis During 1956 in Chicago and Cook County, Illinois, Am. J. Hyg. 70:107, 1959.
7. Siedler, H. D., Kalter, S. S., Thrupp, L. D., Utz, J. P., Finucane, D. L., and Parrott, R. H.: Outbreak of Type 3 Paralytic Poliomyelitis in Washington, D. C., in 1957, Am. J. Hyg. 71:29, 1960.
8. Molner, J. G., Brody, J. A., and Agate, G. H.: Detroit Poliomyelitis Epidemic—1958, J.A.M.A. 169:1838, 1959.
9. Speers, J. F., Chin, T. D. Y., Marine, W. M., Hall, E., and Gravelle, C. R.: Epidemic Poliomyelitis, Des Moines, Iowa—1959, A Preliminary Report, J.A.M.A. 174:864, 1960.
10. Marine, William M., Chin, Tom D. Y., Gravelle, C. R., and Soergel, Marjorie E.: Effectiveness of Salk Vaccine in Reducing Nonparalytic Poliomyelitis in a Large Urban Epidemic, New England J. Med. 264:903, 1961.
11. Harmon, Paul H.: Racial Incidence of Poliomyelitis in the United States with Special Reference to the Negro, J. Infect. Dis. 58:331, 1936.
12. Weston, W., Jr.: Poliomyelitis in South Carolina, 1939, South. M. J. 33:525, 1940.
13. McDaniel, G. E.: Poliomyelitis in South Carolina, 1939. A Preliminary Report, South Carolina M. J. 36:331, 1940.
14. Communicable Disease Center. Age Distribution of Poliomyelitis in the United States in 1956 (Summary Report). Poliomyelitis Surveillance Report Suppl. No. 14, Dec. 6, 1957.
15. Maxcy, Kenneth F.: A Review of the Epidemiology of Acute Anterior Poliomyelitis with Reference to the Mode of Transmission, Journal-Lancet 64:216, 1944.
16. Dauer, Carl C.: The Changing Age Distribution of Paralytic Poliomyelitis, Ann. New York Acad. Sc. 61:943, 1955.
17. Chin, T. D. Y., and Marine, W. M.: Changing Pattern of Poliomyelitis Observed in Two Urban Epidemics, Pub. Health Rep. (In press.)

Preliminary Program

55th Annual Session

Will Appear In

October Issue

Presacral Tumors*

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Presacral tumors may be of greatly varying size and may be asymptomatic. Many are dermoid cysts. The author has reviewed his experience with this group of lesions and outlined the surgical approach to removal.

PRESACRAL TUMORS are lesions found in the potential space formed by the loose attachment of the posterior perirectal fascia and the anterior sacral fibrous coverings. Laterally this area is bounded by the piriformis, coccygeus and levator ani muscles. The latter also forms the floor of this space while the promontory of the sacrum forms its cephalad boundary.

The size of these tumors varies greatly from a centimeter or two to those found occupying most of the true pelvis. Usually the tumors are small. Growth, which is usually slow, may cause the extension of these tumors lateral to the rectum and vagina and proximally into the retroperitoneal abdominal area. The majority are well-encapsulated tumors and consequently the symptoms complained of by the patients are secondary to pressure on the surrounding pelvic structures. Constipation and difficulty with micturation are the most common symptoms. It is understandable that the majority of these tumors, because of their small size, will give few or no symptoms. It has been our experience that most of the tumors seen in this series were discovered at routine rectal examination by the referring physician or by us.

The first medical report of the presacral tumor was written by Middledorpf in 1885,[1] and consequently his name was used to designate the tumors found in this area. They have most frequently been reported as occurring in children and to have a teratomatous origin. They are also most common in women.

Clinical Study

In this series, 26 cases of presacral tumors are reported which gives an incidence of one in a thousand cases seen in a clinic specializing in surgery of the intestinal tract. Most of the tumors found were in adults and the most common pathologic diagnosis was that of dermoid cyst (Table 1).

Rowe and Brock[2] give a complete classification of these tumors and our cases have been grouped accordingly (Table 2).

As is evident in table 2, of the 26 cases diagnosed as presacral tumors, over 50%, or 14 were dermoids or developmental cysts (also called epithelial, epidermoid, cysthydradenoma, sacrococcygeal or coccygeal cysts). Only elements of one germinal layer (ectoderm) could be found taking part in the formation of these cystic structures.[11] The average age in these cases was 36. The youngest was one week old

TABLE 1

CLASSIFICATION AND PATHOLOGY

I.	*Congenital*
	A. Chordoma
	B. Dermoid and developmental cysts
	C. Teratoma
	D. Anterior meningocele
	E. Ectopic kidney
II.	*Neurogenic*
	A. Ependymoma
	B. Neurofibroma
	C. Neurilemmoma
	D. Ganglioneuroma
	E. Paraganglioma
III.	*Osseous*
	A. Giant cell tumor
	B. Osteogenic sarcoma
	C. Chondroma and chondrosarcoma
	D. Osteoma
IV.	*Fibrogenic*
	A. Fibroma and fibrosarcoma
V.	*Myogenic*
	A. Leiomyoma and leiomyosarcoma
VI.	*Inflammatory*
	A. Abscess
	B. Granuloma
VII.	*Miscellaneous*
	A. Lymphoblastoma
	B. Lipoma
	C. Hemangio-endothelioma
	D. Metastatic carcinoma
	E. Ovarian cyst
	F. Hypernephroma
	G. Adenomyoma

*Read before the Section on Proctology, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

TABLE 2

I. Congenital	
A. Dermoid and developmental cysts, all benign	14
B. Teratoma	
1. Benign	3
2. Malignant	1
II. Myogenic	
A. Leiomyoma	1
III. Inflammatory	
A. Cystic granuloma	5
B. Pilonidal granuloma	1
C. Organized hematoma	1
Total	26

and the oldest was 68 years old. Females predominated 2:1. The average diameter of these tumors was 3 cm. (smallest 2 cm., largest 5 cm.). They were encapsulated, unilocular if small. The largest ones tended to be multilocular, and could easily be separated from the surrounding tissues. They were filled with a thick mucilagenous or mucosebaceous fluid, and if not ruptured their removal was a fairly easy procedure. Extirpation of the coccyx was not necessary as a rule, but did aid in the removal of these tumors when they were adherent to the coccyx or posterior rectal wall as the following case illustrates.

Case 1. The patient was a 38 year old woman whose obstetrician discovered a rectal tumor at the time of the delivery of her only child. No difficulty occurred during the delivery. No symptoms or signs referable to the tumor or rectum had been noticed by this patient. Examination of the rectum and sigmoid colon by digital, anoscopy and sigmoidoscopy demonstrated a round, tender, rubbery mass measuring about 5 cm. in diameter and located in the presacrococcygeal area. The rectal mucous membrane was free of any attachments to the tumor, but the latter seemed to be attached firmly to the anterior surface of the lower sacrum and upper coccyx posteriorly and to the rectal muscle anteriorly.

At operation, a midline sacrococcygeal incision extending from the lower two sacral segments to the external subcutaneous sphincter was made. The coccyx was removed and the tumor excised after difficult separation of the tumor from the anterior sacral fascia and the rectal muscle. Drainage to the cavity was established and the wound closed primarily.

Postoperative convalescence was uneventful. Upon inquiry 3 years later, the patient was asymptomatic and there was no evidence of further cyst formation. The pathologic diagnosis in this case was *benign multiloculated dermoid cyst* (Figs. 1-3).

There were 4 cases of teratoma in the series, and in these patients we found the only instance with malignant degeneration. These tumors were cystic, multilocular, possessed thicker walls and were larger than the average

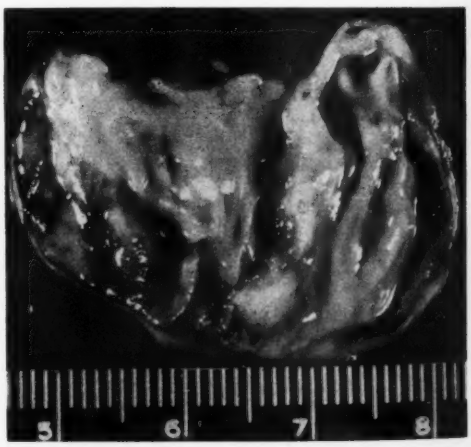
FIG. 1

Typical gross appearance of dermoid. Outer surface.

dermoid cyst. Two benign instances, not reported in detail later, occurred in women each of 49 years. They had a diameter of around 4 cm. and were removed with coccygectomy. The finding of more than one germinal layer in the composition of the tumor led to the diagnosis of teratoma. Primary closure with drainage after approximation of the divided anococcygeal musculature resulted in adequate healing without complications, even though one of the tumors was ruptured upon attempting to separate it from the posterior rectal wall (Fig. 4).

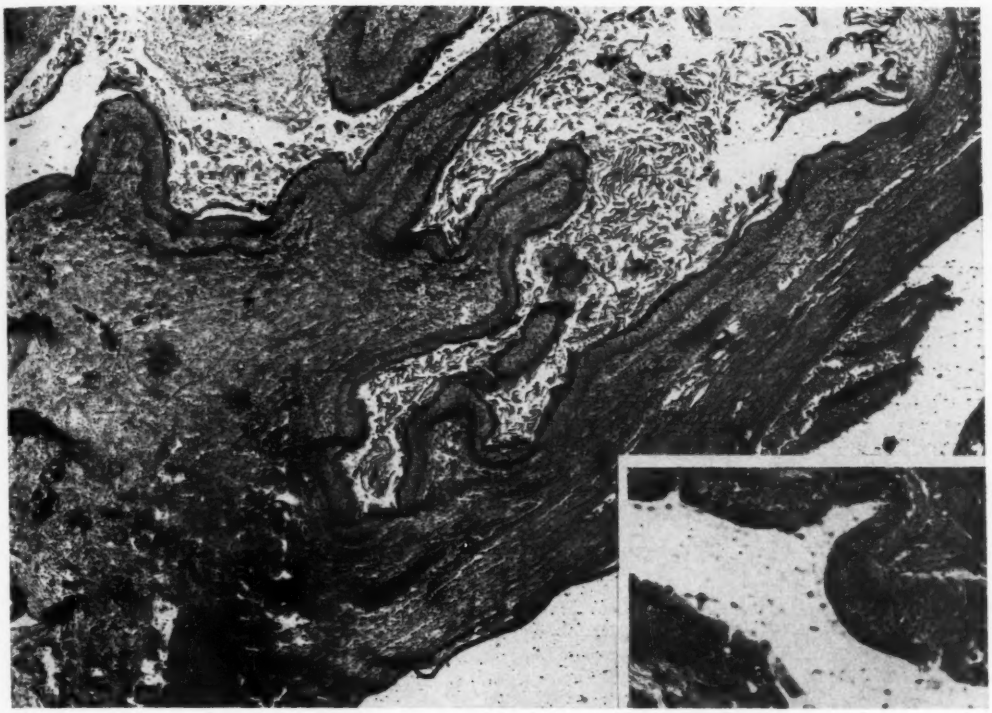
A detailed description of the other two cases

FIG. 2



Typical gross appearance of dermoid. Sectioned.

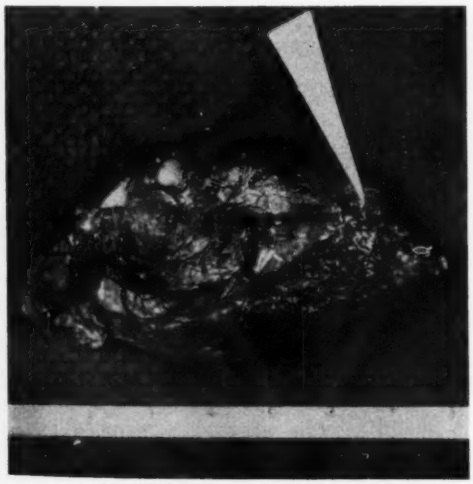
FIG. 3



Microscopic appearance of dermoid (31 x and 200 x).

follow; one in a child representing the more usual case of teratoma reported in the literature,[4,12] while the other demonstrates the rare occurrence of malignant teratoma in an adult male.[6-8]

FIG. 4



Gross appearance of teratoma with hair.

Case 2. A white child was first seen in 1940 when he was 22 months old. A history of diarrhea shortly after birth, with gradual reversion to constipation and eventual development of fecal impactions was obtained. He had had innumerable colonic irrigations to cope with this problem. Digital rectal examination showed the presence of a mass in the cul-de-sac the size and shape of a "tennis ball." There was also noted a stricture at the level of the internal sphincter which would, however, admit the examiner's index finger. Barium enema demonstrated the presence of megacolon from the splenic flexure to, and including the rectum. The bony pelvis was seen to be deficient in the development of the "left half of the bodies and the left neural arches of the 2nd, 3rd, 4th and 5th sacral segments" (Figs. 5 and 6).

The mass was thought to be a congenital tumor and surgical exploration was recommended. For one reason or another this was not performed, but the child was seen at yearly intervals for the next 4 years. The clinical note of 1944 states that the mass had decreased in size to 7.5 cm. in diameter, and seemed to be flat, more than round, against the sacrum. Bowel and urinary functions appeared to be normal. He was again seen 6 years later in 1951 because of repeated fecal impactions and megacolon.

A neurological consultation at this time failed to

FIG. 5

AP roentgenogram showing sacral bony defect on left side. Case of teratoma in a 5 year old child.

reveal any abnormal findings. Exploration and removal of the presacral mass was again recommended and was carried out on July 20, 1951. A sacral incision was made one inch to the left of the midline. The congenitally absent sacral segments were found to be replaced by a thick layer of fibrous tissue. The tumor was exposed anterior to this anomaly and dissected free posteriorly and laterally from the sacral fascia. Some difficulty was encountered anteriorly, because firm adhesions were present between the capsule of the tumor and the posterior rectal wall. With a guiding finger in the rectum it was possible to carry out the dissection without entering the rectal lumen. A strong adhesive band at the level of the internal sphincter was divided. The final attachment seemed to connect the tumor with the filium terminale. On dividing it cerebrospinal fluid leaked from an opening in this stalk. The leak was successfully controlled by ligature and suturing several muscle stamps *in situ*. The wound was closed primarily and the cavity drained. Immediate postoperative convalescence was uneventful. The incision healed in 3 weeks (Figs. 7 and 8).

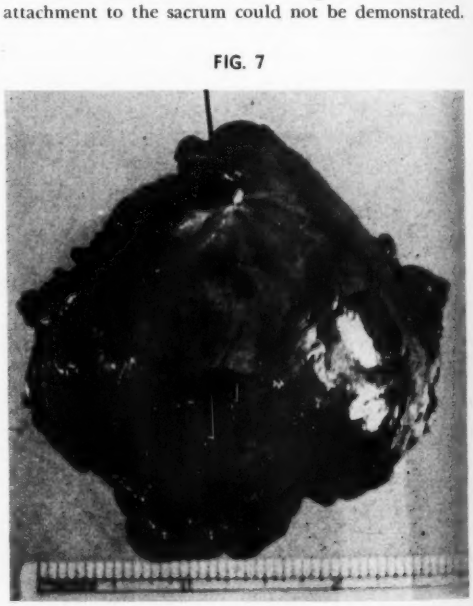
For the next year this child had alternating difficulty with bowel elimination and control, as well as stress incontinence. When last seen in December of 1952, the bowel movements were spontaneous, almost daily, and control of both feces and urine appeared to be normal. The pathologic diagnosis was a *benign teratoma* with "embryonal neurogenous tissue, mucous glands and numerous foci of transitional epithelium . . . at least two germ layers are represented" (Fig. 9).

Case 3. A 47 year old white man who, on routine physical examination by his physician, was found to have a presacral mass. No symptoms were referable to the tumor or the rectal region. As an infant the patient's mother noticed "a lump" posterior to the anus which "disappeared as he grew bigger." Digital rectal examination and sigmoidoscopy in February of this year disclosed a presacral, cystic round tumor mass about 8 cm. in diameter. It seemed to be firmly attached to the muscularis of the rectum, but the mucous membrane rode over it on digital examination; attachment to the sacrum could not be demonstrated.

FIG. 6

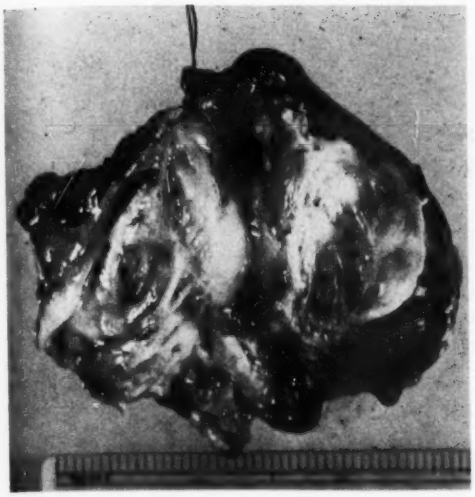
(Case 2) Barium enema showing filling defect in left sacral area due to teratoma.

FIG. 7



(Case 2) Gross surface appearance.

FIG. 8



(Case 2) Gross appearance on section.

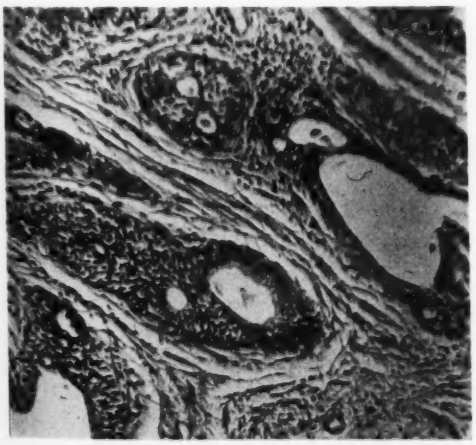
Two weeks later a large multilocular cystic tumor was removed at operation. There was no difficulty separating it from the anterior wall of the sacrum after coccygectomy, but it was so firmly attached to the posterior wall of the rectum that some of the cysts were ruptured in the attempt at removal of the tumor. Several small, hard areas were evident on gross examination; the cysts were filled with sebaceous thick fluid. The wound was closed after drainage of the presacral space.

After prolonged pathologic consultation, involving several pathologists, the diagnosis was returned as *teratoma with areas of malignant degeneration* (Fig. 10).

One pathologist was in favor of the origin of the malignancy "in some embryonal remains, preferably mesonephros." Because a cyst was ruptured at the time of the operation with the possibility of having spread cancer cells in the operative wound, it was thought best to do a wider excision of the involved area. This was done 6 weeks after the primary operation. Resection of the last two sacral segments, the anococcygeal raphe, the old scar, the posterior muscle coat of the rectum involved by scar tissue and the posterior one third of the right levator ani and adjoining ischiorectal fat was done. Pathologic study failed to reveal any cancerous growth in any of the tissues removed. The wound was closed primarily in part but, because of the extent of the operation, about one third of it was left to heal by secondary intention. Healing was delayed but complete in 2 months. Roentgen therapy was advised and carried out when the wound healed.

Frequent check-up examinations failed to disclose any abnormal findings until 3 months later when a hard 2 cm. nodule was definitely felt in the scar tissue to the right of the rectum. Biopsy of this area showed a recurrence of the carcinoma. Therefore, an abdominoperineal excision was decided upon and carried out on Sept. 26, 1960. Exploration of the abdomen was normal, no evidence of spread could be felt at this stage of the operation. The right hypogastric artery was ligated and the adipose and lymphatic tissues surrounding this vessel and in the right obturator area were excised. No metastases were found in these structures. The wide perineal resection included the anus, the sacral scar, the rectum, the area of biopsy and surrounding ischiorectal fat and skin, and most of the puborectalis portion of the levator ani. At the termination of the resection it was evident that no abnormal indurated areas had been left in the perineal tissues. Several block biopsies of the edges of dissection showed the tissues apparently to be normal. Convalescence was uneventful, but because of the technical inability to close the perineal defect it will be some time before complete closure can be anticipated.

FIG. 9

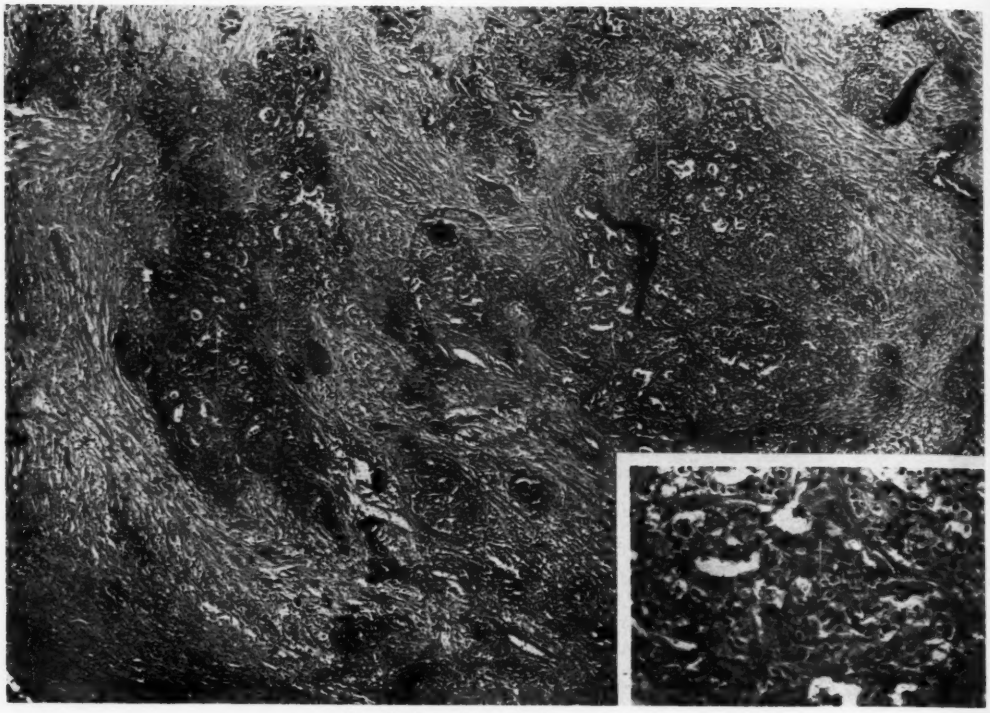


(Case 2) Photomicrograph of specimen showing glandular elements.

There was one case in this series, that of a 48 year old man, from whom a tumor was removed and diagnosed pathologically as a leiomyoma. This tumor was 5 cm. in diameter and was found by digital examination to be opposite the third sacral segment behind the rectum. It was freely movable and the rectal mucous membrane was not attached to the growth. It was rubbery in consistency and actually felt like a submucosal type of tumor. It was removed through a sacrococcygeal incision and blunt dissection to, and around the area of the lesion. The tumor was encapsulated and easily removed from the rectal muscularis.

The remaining 7 cases are grouped under inflammatory classification. One occurred in a 78 year old woman and was apparently caused by a rupture in a sacral blood vessel. Fibrous tissue with hemosiderin deposits was found to compose most of the tumor. The other cases had in common the presence of granuloma

FIG. 10



(Case 3) Photomicrograph (31 x and 200 x).

with chronic sinus and abscess formation. The inflammatory process in these cases did not communicate with the posterior anal crypt, but in two a small sinus tract was found between the tumor and an opening in the posterior anal margin. This opening was located where anal dimples are most commonly found. This brings up the possibility of a congenital origin of these cysts, infection destroying the histologic picture. The treatment in these cases consisted in establishing the pathologic nature of the process, removal of all "infected" tissue plus most of the fibrous wall of the tumors and adequate drainage. An unusual case of an inflammatory presacral tumor follows.

Case 4. A 28 year old man, with a history of having had 4 operations for the cure of a pilonidal cyst, had as his chief complaint anal drainage since his last operation 2 years prior to my examination. This showed the presence of a dimple in the anoderm halfway between the mucocutaneous line and the anal margin. Seropurulent material could be seen coming from the opening. There was no evidence of a pilonidal opening external to the anus. Digital rectal examination demonstrated a hard, elongated, fibrous mass measuring about 8 cm. long and 4 cm. in diameter firmly attached to the anterior lower sacrum and coccyx and to the posterior rectal wall. A solid fibrous cord connected

FIG. 11

(Case 4) AP roentgenogram with radiopaque material in the cavity of the cyst.

this mass with the anal opening described above. Probing of this opening could be done to a distance of about 10 cm. (Figs. 11 and 12).

Exploration of the area was difficult because of the large amount of scarring found both posterior and anterior to the sacrum. The last segment of the sacrum and the coccyx were removed after sharp dissection from the mass anteriorly. Separation of the posterior rectal wall could not be done without resection of a posterior segment of the rectum. Consequently, division of the mass was done paralleling the posterior rectal wall to a point opposite the second sacral segment. Transection of the mass was accomplished at this level knowing that some of the fibrous part of the mass was being left *in situ*. Frozen section and pathologic examination showed the presence of hair in a multiloculated mass, honeycombed by numerous sinus tracts. The wound was left open, after repairing the anal sphincter, to prevent further extension of this process. The patient's course was followed for 8 months during which time the wound healed. His only complaint on dismissal was occasional inability to control gas or a liquid stool. The diagnosis in this case was *pilonidal sinus* in the presacral space with foreign body granuloma.

Discussion

It has been our practice in most of the cases of presacral tumors to determine the etiology of the lesions in question[10-13] before attempting definitive surgery. Beside the routine digital rectal and sigmoidoscopic examination carried out on all these patients, x-ray studies of the sacrum were done in all.[14] Occasionally a barium enema was preferred because, as in the case of the child with the teratoma, the bowel symptoms were prominent. Sacral defects are more commonly seen with meningocele,[9] and this anomaly was suspected in that case. Consequently neurosurgic consultation was requested and the neurosurgeon was present at the time of the operation. (Others also believe this to be good cooperative practice.)

FIG. 12

(Case 4) Lateral view.

Needle biopsy of the tumor prior to operation has been recommended,[2] although one must be aware of the possibility of obtaining a benign report by this method if a small area of malignancy is missed. This would have probably been the case in the patient with malignant teratoma, since the tumor was mostly benign and only small areas adjacent to the rectal wall were later, after extensive consultation, found to be of malignant nature. It was disheartening in this case to have subjected this patient to a wider and more radical perineal excision 6 weeks after his original operation, and not find any metastatic spread in the tissues only to find it several months later. The reason behind doing the abdominoperineal extirpation was the dense adhesion between the recurring tumor and the right rectal wall, together with the inability to differentiate grossly between scar tissue and tumor. On detailed microscopic study of the rectal musculature and the surrounding tissues, several foci of metastases were discovered.

The surgical technic involved in the removal of presacral tumors has been described in detail by Rowe and Brock,[2] Shackelford and Rhode[3] and Gross, Clatworthy and Meeker,[4] and will not be repeated at this time. Suffice it to restate that the last two sacral nerves (4th and 5th) can be sacrificed bilaterally, together with their bony beds without causing incontinence of urine or feces. The third sacral nerve may be sacrificed on one side with similar good results. Division of both third sacral nerves will result in incontinence of urine and feces. In the total eradication of large malignant tumors attached to the sacrum above the third sacral segment, it may be necessary to resect most of the sacrum and sacral nerves as in cases of chordoma. The coccyx should be removed in all cases of teratoma, as was brought out by Gross, Clatworthy and Meeker,[4] in their study, "because microscopic rests of neoplastic cells are commonly found in or immediately adjacent to this bone."

The surgical technic in exploration of the presacral space has also been reported by McLean and Arminsky[5] and Larkin.[15] They reported on 34 patients in whom trans-sacral resections of portions of the rectum were performed by using this approach. They divided the sacrum between the fourth and fifth sacral segments. Ample room for the surgical procedures was obtained by this method. This should support the fact that though the rectum may be injured at the time of the removal of the presacral tumor, suture of this organ may be accomplished without much technical difficulty or postoperative complications. It is well to prepare the bowel with prophylactic chemotherapy and antibiotics prior to presacral exploration, in case the rectum is injured during the procedure. This was done in the patients of this series who had the larger tumors.

In discussing Drs. Rowe and Brock's[2] paper on presacral tumors, Dr. W. J. Martin brought out the fact that extensive resection of sacral bone will cause a posterior rectocele through the operative field, which can be quite distressing to the patient. Prevention of this mishap would seem rather difficult in extensive resection of sacral bone.

Summary and Conclusions

Twenty-six instances of lesions diagnosed as presacral tumors are presented. The majority of these were classified as dermoid tumors. Three instances of teratoma found in adults and one in a child are discussed. One case of a malignant teratoma in a 47 year old man is presented in detail.

The diagnosis of these tumors in the adult is usually made at routine physical examination. They are usually symptomless unless the tumor is large enough to cause pressure on surrounding structures.

Treatment consists of total extirpation of the tumor. In cases of teratoma a coccygectomy should be a part of the surgical procedure.

References

1. Middledorpf, K.: Zur Kenntniss der Angebornen Sacralgeschwulste, Virchow's Arch. Path. Anat. 101:37, 1885.
2. Rowe, R. J., and Brock, D. T.: The Surgical Management of Presacral Tumors, Am. J. Surg. 92:710, 1956.
3. Shackelford, R. R., and Rhode, C. M.: Sacrococcygeal Chordoma, Its Surgical Treatment, Ann. Surg. 141:952, 1955.
4. Gross, R. W., Clatworthy, H. W., Jr., and Meeker, I. A., Jr.: Sacrococcygeal Teratomas in Infants and Children; A Report of 40 Cases, Surg. Gynec. & Obst. 92:341, 1951.
5. McLean, D. W., and Arminsky, T. C.: Trans-sacral Resection of the Rectum, Dis. Colon & Rectum 2:534, 1959.
6. Palumbo, L. T., Cross, K. R., and Paul, R. E.: Sacrococcygeal Teratomas; Review of the Literature; Report of a Case in an Adult Containing a Glomus, Ann. Surg. 113:421, 1951.
7. Lisco, H.: Malignant Tumors Developing in Sacrococcygeal Teratoma, Ann. Surg. 115:378, 1942.
8. Brindley, G. V.: Sacral and Presacral Tumors, Ann. Surg. 121:721, 1945.
9. Briggs, J. D., and Edwards, B. F.: Anterior Sacral Meningocele, California Med. 78:59, 1953.
10. Mayo, C. W., Baker, G. S., and Smith, L. R.: Presacral Tumors; Differential Diagnosis and Report of a Case, Proc. Staff. Meet. Mayo Clin. 28:616, 1953.
11. Colcock, B. P., Sass, R. E., and Standinger, L.: Dermoid Cysts, New England J. Med. 252:373, 1955.
12. Hickey, R. C., and Layton, J. M.: Sacrococcygeal Teratoma; Emphasis on the Biological History and Early Therapy, Cancer 7:1031, 1954.
13. Laird, D. R.: Presacral Cystic Tumors, Am. J. Surg. 88:793, 1954.
14. Utne, J. R., and Pugh, D. G.: Roentgenological Aspects of Chordoma, Am. J. Surg. 90:775, 1955.
15. Larkin, M. A.: Trans-sphincteric Removal of Rectal Tumors, Dis. Colon & Rectum 2:446, 1959.

Discussion (Abstract)

Dr. Patrick H. Hanley, New Orleans, La. Dr. Robert Rowe, who was the original discussant of Dr. Castro's paper, was unable to be here and it is with pleasure that I open this discussion. Dr. Castro is to be congratulated on his excellent presentation and the description of his experience with presacral tumors. Because of the infrequent occurrence of these tumors, individual experience is limited and we have all profited by such an excellent presentation on this interesting, rare, proctologic problem.

Since Middledorpf's description of sacrococcygeal teratoma in 1885, many varieties of presacral tumors have been referred to as Middledorpf's tumors. As in all neoplasms, if one adheres to the histologic diagnosis for classification, as Dr. Castro did, a more accurate understanding of the pathology and preferred surgical treatment will be obtained.

In our experience, as in Dr. Castro's, epidermoid inclusion cysts have been the most frequent tumors encountered. Most of them were intimately attached to the posterior musculature of the lower portion of the rectum and sphincteric muscles, in one of which the attachment extended to the mucosa. Not all epidermoid inclusion cysts are as intimately attached to the rectal and sphincteric musculature as was Dr. Castro's second case, which had a final attachment to the filum terminale. We had a similar instance in a child aged 6 years. The cyst actually originated in the sacral canal, growing into the presacral space; pressure on the cyst at defecation or on palpation caused pain. The urinary and intestinal dysfunction was probably due to pressure on the sacral nerves in the sacral canal. These two cases seem to support the belief that some epidermoid cysts might originate from vestigial remnants of the neurenteric canal.

Another of our interesting patients was an 18 year old white girl in whom an epidermoid inclusion cyst was discovered on routine examination for pain along the medial aspect of the thigh. The epidermoid cyst, approximately 8 cm. in diameter, was located high in the true pelvis and posterolateral to the rectum. We believed that the obturator-like distribution of pain was not due to the inclusion cyst. Since she had recently been married and the cyst was not causing symptoms, we decided to observe it. We saw her periodically through three pregnancies, during which time the cyst grew somewhat. During the third labor a

needle was inserted into the cyst, decompressing it. The exudate was sent to the pathologist, who confirmed the diagnosis by reporting that the cyst contained debris and desquamated epithelial cells. Because this tumor was located high in the pelvis, a transabdominal approach was used to free it from the rectum and adjacent structures, with the idea that upon closure of this wound the cyst would be removed immediately through a parasacral coccygeal approach.

At abdominal operation, after the rectum was mobilized from the sacrum, as for abdominoperineal resection, the cyst was easily isolated, and although the operative field was deep, the tumor was readily excised.

Presacral epidermoids may rupture along the side of the anus and simulate a fistula-in-ano. Material for histologic diagnosis may be obtained by introduction of a catheter into the opening. Injection of Diodrast into the sinus and inflation of the rectum with air will help to locate the lesion and rule out rectal connections. Some cysts may protrude under the perianal skin and actually represent dumbbell-shaped cysts with the greater part above the levators. The parasacral coccygeal incision may extend to one side of the anal sphincter, and in some cases a U-shaped incision, cutting the anococcygeal ligament, may be of some advantage. Removal of the coccyx is frequently not necessary, as Dr. Castro mentioned.

Teratoma is the commonest large tumor in infants, and in 90% it is evident externally, as in Dr. Castro's Case 3. The incidence of malignant degeneration is as high as 27%, and this increases if the tumor is not removed soon after it is detected during infancy, as was the unfortunate outcome in this case.

One of our most interesting presacral tumors was recently seen in a white woman 50 years old. On digital examination two round nodules connected by a band of tissue were felt, one apparently in the rectal wall and the other in the presacral space on the left side. The lesion appeared to be fixed to the presacral fascia on palpation. A needle was inserted into the tumor through the rectal wall for biopsy. The tissue obtained was suspected to be carcinoid, and on abdominal exploration, the whole mass was easily freed from the sacrum; abdominoperineal resection was accomplished without too much difficulty. The final diagnosis was metastatic epidermoid carcinoma. The primary site was never determined. This case is presented as another possibility of presacral tumors.

It was a pleasure to have the privilege of discussing Dr. Castro's paper.

Dr. Castro (Closing). I want to thank Dr. Patrick Hanley for his interest and his remarks on this paper.

He mentioned the abdominal approach for the extirpation of some presacral tumors as in the case presented by him. I am in full agreement with that if the tumor, on careful examination, seems to be high in the presacral space, near the promontory of the sacrum, or if unusually large and occupying a pelvic position, an abdominal approach would seem the wiser method. Fortunately in our cases we did not have to resort to an abdominal operation for the primary removal of these tumors.

Viral Hepatitis: Experience in a General Civilian Hospital

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Contrary to a commonly accepted attitude of the past that hepatitis was a relatively benign disease, present knowledge indicates a need for respect for this infection and concern as to possible residual hepatic damage.

VIRAL HEPATITIS is usually considered to be an infectious disease of mild severity, with minimal mortality and morbidity rates. However, experience in a general civilian hospital suggests that this may not always be true. This paper summarizes experience with 207 patients, 137 of whom had acute infectious hepatitis, designated IH, and 73 homologous serum jaundice or serum hepatitis, designated SH, seen at the Ochsner Clinic from 1942 to 1959; 3 patients had both diseases at different times. The results of this study emphasize the relatively serious nature of viral hepatitis in a general hospital, especially the acute complications—hepatic failure and death—and the primary sequelae of chronic hepatic disease. Only those cases that satisfied the usual clinical and laboratory criteria for acute infectious hepatitis and in which adequate differential data excluded diagnoses of infectious mononucleosis, amebic hepatitis, leptospirosis, brucellosis, mechanical obstruction, and toxic hepatitis were included. Pathologic diagnosis obtained from needle biopsy and surgical exploration was relied upon in uncertain cases. IH was differentiated from SH by history of receipt of blood transfusion or suspected contaminated injection 6 weeks to 6 months before onset of the illness.

Cholestatic or cholangiolitic hepatitis was characterized by an indolent course, pruritus, hepatic function tests indicating cholestasis, and a biopsy report of cholestasis with pericholangiolar inflammatory activity but little parenchymal reaction. Cases were classified as chronic hepatitis if the patient had continuing activity for more than 4 months, with clinical and laboratory evidence of hepatic cell damage, and a pathologic diagnosis of periportal and lobular inflammation with continuing hepatocellular reaction without cirrhosis. Cases were classified as postnecrotic cirrhosis if the usual stigmata of cirrhosis developed after an attack of viral hepatitis or if the histologic picture was one of invasive periportal fibrosis with fibrous connections of portal spaces to each other and to central veins, eccentric central veins, and typical regenerative nodules of variable size separated by narrow and broad bands of fibrosis.

Results

Age. The patients in this series were considerably older than those in commonly reported series (Table 1).[1,2] More than one half of the patients with IH were older than 40 years, almost one third being older than 50 years. About two thirds of the patients with SH were older than 40 years and one third older than 50. This is similar to the experience of others, with the exception of inoculation epidemics in the Armed Forces, which are, of course, related to passage of infected material from patient to

TABLE 1

DISTRIBUTION OF 207 PATIENTS WITH VIRAL HEPATITIS ACCORDING TO AGE

Age (Years)	*Infectious Hepatitis*	*Homologous Serum Jaundice*
0-9	3	0
10-19	4	2
20-29	26	7
30-39	30	11
40-49	34	21
50-59	20	15
60-69	16	13
70-79	2	3

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patient during treatment of or immunization against other diseases.

Sex. There were 94 males and 43 females with IH, whereas Paul[3] reported an equal sex distribution except for mothers in the childbearing age, who acquired infectious hepatitis at a slightly higher rate than men of comparable age. On the other hand, in our series, SH affected women with somewhat greater frequency than men (30 males, 43 females); this is perhaps related to a greater incidence of operations and blood transfusions in this group, although figures are not available to substantiate this.

Clinical manifestations included, for the most part, the well-recognized malaise, anorexia, jaundice, and usually aching, rarely severe pain in the right upper abdominal quadrant (Table 2). Headache was common and, although fever was often present and of low grade, occasionally high fever with associated chills was noted. The picture of acute gastroenteritis was occasionally present, with diarrhea associated with anorexia and vomiting. Pruritus was present often enough to exclude its usefulness as a differential criterion from patients with obstructive jaundice. Examination most commonly revealed a large, tender liver and jaundice, with occasionally a palpable spleen. When sought for, a small, soft, solitary lymph node located low in the right posterior cervical chain at the level of the right seventh transverse cervical process was often present and of considerable differential diagnostic help. This has been referred to as the "hepatitis node." Bilateral cervical adenopathy, however, was common as was adenopathy in other sites. Edema and ascites, though uncommon, when present were evidence of a relatively severe pathologic process, but did not necessarily indicate a poor prognosis. Cutaneous lesions were most often secondary to scratching, but occasionally a true exanthem was noted.

TABLE 2

RELATIVE FREQUENCY OF OCCURRENCE OF RECORDED CLINICAL MANIFESTATIONS IN 207 PATIENTS WITH ACUTE VIRAL HEPATITIS

Manifestation	*Per Cent*
Malaise	98
Jaundice	94
Anorexia	87
Hepatomegaly	87
Tender liver	85
Dark urine and/or light stools	81
Nausea with or without vomiting	74
Abdominal pain	65
Headache	62
Fever	60
Weight loss	48
Diarrhea	40
Splenomegaly	22
Pruritus	20
Constipation	15
"Hepatitis node"	12
Cutaneous lesions	8
Edema	7
Decreased taste for cigarettes	7
Bleeding tendency	6
Ascites	6
Tender spleen	5

Course and Outcome. Only 67% of the patients in this series recovered uneventfully; the remaining 33% had complications. Ten per cent died.

The complications were much the same in both IH and SH groups. One patient with SH exhibited a severe fulminant course with hepatic coma but completely recovered. Eleven patients had severe fulminant or rapidly progressive courses with hepatic coma terminating in death. Six of these were women and the average age was 49 years with a range of 27 to 68 years. The duration of illness ranged from 10 days to 12 weeks, with an average of 6 weeks. Death was caused by hepatic failure in 9 patients, gastrointestinal bleeding in 1, and hepatic failure and gastrointestinal bleeding in one. Major surgical procedures contributed to the fatal outcome in 3 patients and gastrointestinal bleeding in 2 others. In these 2, bleeding was generalized, one suffering from afibrinogenemia and the other concomitant acute bacterial endocarditis. No specific origin of the bleeding could be found at necropsy. Other associated factors included carcinoma in 2 patients, pregnancy (the last trimester) in 2, and severe diverticulosis and diverticulitis of the colon with perforation, recurrent intestinal obstruction, and concurrent amebic hepatitis in one each. Necropsy was performed in 8 cases and postmortem needle biopsy of the liver in one. Severe necrosis and parenchymal collapse with varying degrees of regeneration were prominent features in 8 of the 9, and in one the pathologic picture was that of cholangiolitic hepatitis. In another, early postnecrotic cirrhosis was present in addition to the severe acute hepatitis.

Fifteen patients (10 males and 5 females) had acute illness of variable intensity with the clinical picture and pathologic features of cholestatic disease. Their ages ranged from 37 to 68 years, averaging fifty-two. Jaundice lasted from

8 weeks to 23 months. Nine had severe itching and in all the serum alkaline phosphatase level was greatly elevated. Serum cholesterol was elevated in 6 of 8 patients, and in the 12 cases in which biopsy was done the characteristic noninflammatory cholestasis was demonstrated. Eight patients underwent surgical exploration; 3 died after operation. Two other patients died, one from hepatic coma and one from recurrent gastrointestinal bleeding, which was determined by esophagoscopic examination to be unrelated to esophageal varices. This patient also had familial telangiectasia of the gastrointestinal tract. The duration of hepatic disease from onset to death in this group was from 8 weeks to 23 months, averaging 10½ months. Two of these patients are included in other categories. One had postnecrotic cirrhosis and the other a fulminant fatal course after exploration of the biliary tract. Postmortem examination was performed in both of these cases. Seven patients recovered, apparently completely, but the remaining 3 still had hepatitis when last seen.

Thirty-six patients (25 males and 11 females) had acute viral hepatitis followed at varying intervals by postnecrotic cirrhosis. This group ranged in age from 17 to 75 years, with an average age of 43 years. Twenty-five exhibited enlarged livers and only 2 had small livers. Persistent jaundice was noted in only 3 patients, but 12 had recurrent icterus. Approximately one third of the patients had splenomegaly and ascites, and loss of weight, when present, was often profound. Spider angiomas, edema, increased abdominal collateral veins, gynecomastia, palmar erythema, and pleural effusion were less frequent.

Seven patients had esophagoscopy, 3 of whom were seen to have esophageal varices at intervals of 18 months, 2½ years and 15 years from the onset of hepatitis. Diagnosis was established by histologic examination of the liver in every patient from 3 weeks to 13½ years after onset. Most cases, however, were confirmed pathologically 1 to 6 months after the onset of viral hepatitis.

The laboratory tests whose results remained abnormal longest were the bromsulfalein, which was most persistent in 71% of instances, the thymol turbidity in 64%, the serum bilirubin in 48%, and albumin-globulin ratio in 45 per cent. The thymol and bromsulfalein values characteristically were persistently elevated, whereas the bilirubin level fluctuated.[4,5] Serum transaminase determinations were available in only 8 of the later cases, but were all significantly elevated at intervals ranging from 2½ months to 13 years from the onset of illness. Of importance in these cases is the fact that nearly always the results of more than one test were abnormal.

Six patients with postnecrotic cirrhosis died, 5 from the hepatic disease. These 6 patients ranged in age from 20 to 51 years. Causes of death were hepatic coma in 3 and gastrointestinal bleeding in two. Postmortem examination was not performed in these latter 2 so the actual site of bleeding could not be ascertained. Congestive heart failure contributed significantly to the death of one patient in this group. Another patient had a course typical of severe fulminant hepatitis, as previously noted, but at necropsy, in addition, exhibited early active postnecrotic cirrhosis. Also, as previously noted, still another patient at necropsy had histologic features of cholestatic disease as well as postnecrotic cirrhosis. In the patients who died with postnecrotic cirrhosis, the duration of illness ranged from 7 weeks to 3½ years.

Twenty of the 36 patients have had continuing hepatic disease up to this writing, the total duration ranging up to 15 years. Ten patients are considered to be clinically recovered in that there is no present evidence of activity of hepatic disease, but microscopic sections of the liver reveal varying degrees of regenerated hepatic parenchyma with minimal to moderate fibrosis and no inflammatory activity.

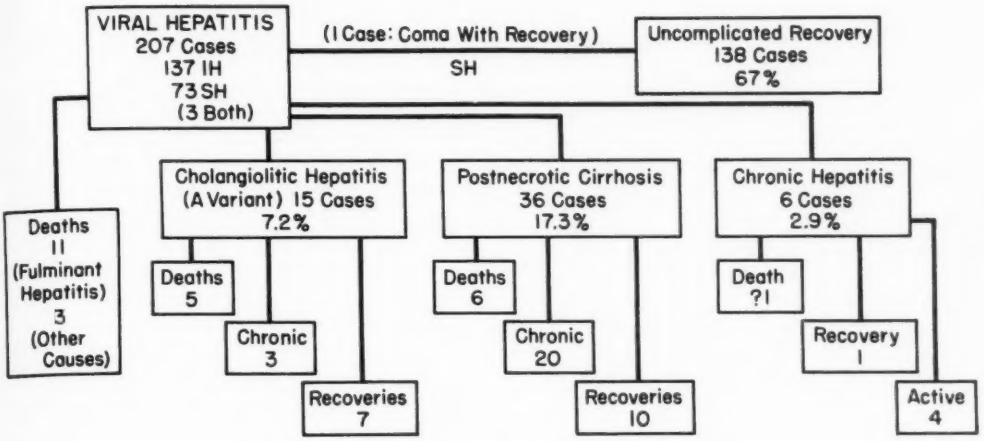
Six patients had chronic hepatitis with evidence of continuing hepatic disease lasting longer than 4 months, but with as yet no good evidence of cirrhosis. These patients ranged in age from 41 to 72 years with an average of fifty-seven. One patient is probably dead as, when last seen 5 months after the onset of illness, he had hepatic coma. Another patient, after 4 years of apparently abnormal hepatic function, has recovered fully.

Figure 1 is a schematic diagram of the course of illness in our 207 patients and emphasizes again the significant mortality and morbidity rates of the disease in a general civilian population.

Comment

The important features of this study are the significant mortality rate, high morbidity rate, and frequent sequelae of viral hepatitis occurring in a civilian general hospital population.

FIG. 1



Diagrammatic representation of fate of 207 cases of viral hepatitis.

They are due largely to other existing illness, including pre-existing hepatic disease, to the necessity for operation in the presence of jaundice, to the presence of hepatitis complicating pregnancy, and to the advanced age of most of this group of patients. Mortality rates in the usual reported series of infectious hepatitis are 0.05% or less,[6] whereas the mortality rate in the present series is approximately 20 times greater. The higher mortality rate in pregnancy was noted by Viswanathan[7] in the New Delhi epidemic of 1955-1956. He reported a general mortality rate of 0.99% but pregnant women were affected three times as frequently as other women, and the mortality rate among the pregnant women was 10 per cent.

Data similar to ours were reported by Thaler and co-workers[8] in their study of 594 cases of homologous serum jaundice between 1946 and 1949. Their mortality rate was 9.3%, and during a 3½ year follow-up period they found postnecrotic cirrhosis in an additional 3.5 per cent. Kunkel and associates[9] noted abnormally prolonged, complicated convalescence in 17% of 350 patients with acute IH but most of these were simple relapses with ultimate recovery. However, at the end of one year 2.3% had not recovered completely.

Cullinan and co-workers[10] conducted a long-term follow-up study of 1,293 cases of viral jaundice occurring in the British forces in World War II. The mortality rate was 0.28% and the recurrence rate during the subsequent years was 8.3 per cent. In 3.2% ill health lasted as long as 7 years but no cases of postnecrotic cirrhosis were found.

Neefe,[11] in reviewing a large amount of collected data, estimated that chronic hepatitis developed in 0.6% of icteric cases, including postnecrotic cirrhosis, cholestatic hepatitis and simple chronic hepatitis. MacDonald and Mallory[4] postulated development of postnecrotic cirrhosis subsequent to 0.7% of all cases of viral hepatitis and suggested a recovery rate of about 99 per cent.

These figures again are at variance with those reported in the present study. The incidence of cholestatic hepatitis has not been established, but it appears that this diagnosis may be made in a significant number of cases of viral hepatitis. Eliakim and Rachmilewitz,[12] specifically searching for cholestatic hepatitis in a series of 104 cases of viral hepatitis, found this lesion in 23 per cent. Additionally, Dubin and co-workers[13] reported an epidemic at Fort Sam Houston in which the cases were predominantly those of cholestatic hepatitis. In our series only 7.2% presented these characteristics.

Illustrative Cases

The following illustrate the particular problems encountered in the management of our patients.

Case 1. A 41 year old white woman with known postnecrotic cirrhosis was admitted to the hospital for elective portacaval shunt. Hepatic function abnormalities included bromsulfalein retention 22%, thymol turbidity 16.5 units, serum albumin-globulin ratio 3.9/7.9, serum alkaline phosphatase 10.9 units, but normal

serum bilirubin. A mild episode of gastrointestinal bleeding occurred in the hospital, but after blood transfusions were given, a portacaval shunt was carried out on May 20, 1958. Surgical liver biopsy revealed typical postnecrotic cirrhosis and scarring. After an uneventful postoperative course, the patient was discharged.

She was readmitted on July 30, 1958, because of weakness, fever, anorexia, nausea, vomiting, and jaundice of one days duration. Results of laboratory studies were typical of the findings in acute viral hepatitis or acute hepatocellular damage, with 9,900 WBC. per cu. ml., 52% lymphocytes, serum bilirubin 5.3 mg. per 100 ml., serum glutamic oxalacetic transaminase (SGOT), 2,000 units, serum glutamic pyruvic transaminase, 3,817 units, and bromsulfalein retention of 43 per cent. Within 2 days the SGOT had reached 6,810 units and the serum bilirubin 20 mg. per 100 ml. Fortunately, though her course was rather stormy, she recovered, and her condition returned to approximately her former status of compensated postnecrotic cirrhosis.

This case illustrates the danger of superimposition of viral hepatitis (homologous serum jaundice) upon previously existing cirrhosis.

Case 2. A 44 year old white man was admitted on July 2, 1956, because of nondescript abdominal pain, generalized malaise, and jaundice of 6 weeks' duration. His liver was enlarged to 6 cm. below the right costal margin and was soft and tender. Laboratory studies were nonpredictive, and because of the possibility of extrahepatic obstruction, the abdomen was explored; the biliary tree appeared normal. Transfusion of one liter of whole blood was given during the operation. Biopsy of the liver revealed moderate periportal inflammation, and a few pericentral bile thrombi with minimal parenchymal reaction (Fig. 2,A).

Postoperatively, the patient improved progressively, but on Sept. 4, 1956, he was again seized with profound anorexia, malaise, pronounced exacerbation of jaundice and biliuria. Laboratory tests revealed evidence of extensive parenchymal cellular damage with total serum bilirubin of 15.7 mg. per 100 ml., bromsulfalein retention of 55%, cephalin flocculation 4+, thymol turbidity 16.7, and serum glutamic oxalacetic transaminase 2,085 units. Gradual improvement occurred and liver biopsy performed on Oct. 30, 1956, revealed nodular regeneration and increase in portal inflammation, less bile stasis, and more regenerative activity than in the previous specimen. The picture suggested processes of two different stages, including mild postnecrotic cirrhosis (Fig. 2,B). Subsequent studies have revealed no evidence of residual hepatic difficulty.

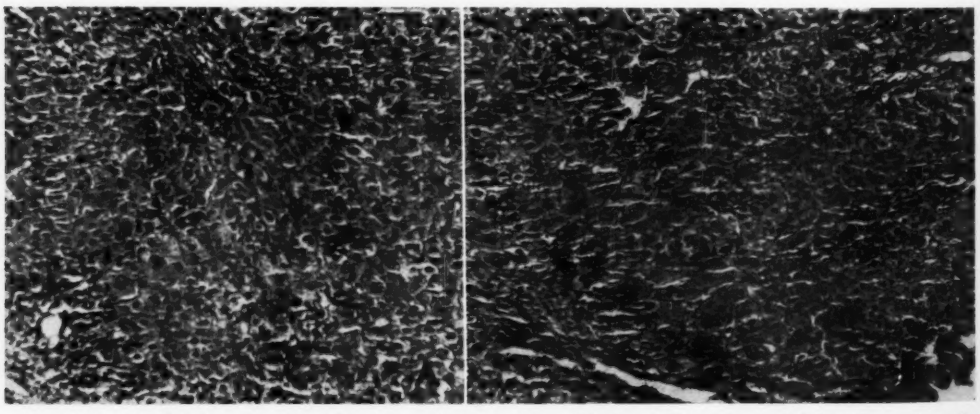
It is our opinion that this case represents cholangiolitic hepatitis complicated by subsequent development of homologous serum jaundice attributed to blood transfusion administered during operation.

Case 3. A 52 year old white man was admitted Oct. 21, 1957, because of dyspepsia, jaundice, and slight loss of weight for the preceding 6 weeks. The liver was easily palpated but was not tender. Laboratory studies suggested severe but not acute hepatic parenchymal damage. Liver biopsy on October 28 revealed pronounced necrosis and stromal collapse, regenerating hepatic parenchyma, and severe inflammatory activity (Fig. 3,A). Moderate subjective improvement occurred with diminution of jaundice but increasing hepatomegaly, vascular spiders, a palpable spleen, and an increase in venous pattern over the abdominal wall developed. Despite intensive rest, dietary support, and administration of prednisone, activity continued and serial needle biopsies revealed development of full-blown postnecrotic cirrhosis, the last needle biopsy having been performed on March 11, 1959 (Fig. 3,B). Esophagoscopy revealed moderate esophageal varices.

This case illustrates direct progression of rather severe hepatitis to well-marked postnecrotic cirrhosis.

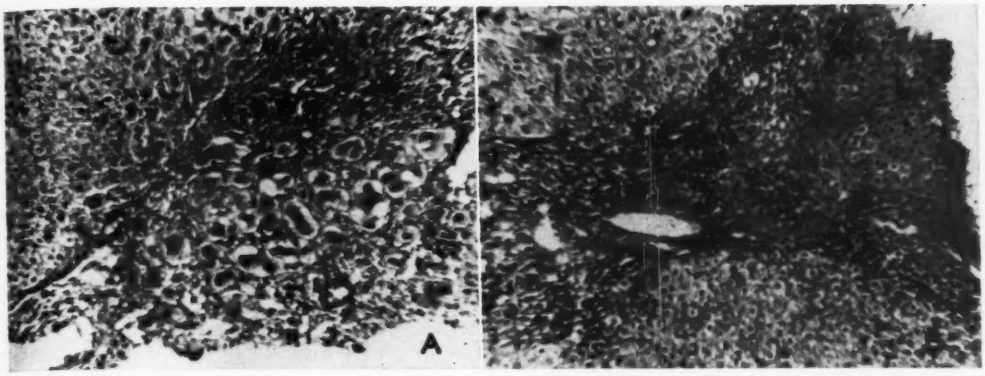
Case 4. A 68 year old white woman was admitted to the hospital on Feb. 6, 1959, because of nausea, vomiting, jaundice, and itching of one months duration, but no pain. Physical examination revealed many excoriations and scattered ecchymoses of the skin. The liver

FIG. 2



(Case 2) (A) Initial biopsy showing minimal parenchymal reaction. (B) Second biopsy showing lobular inflammation and necrosis.

FIG. 3



(Case 3) (A) Initial biopsy showing severe inflammation, necrosis and regeneration. (B) Fourth biopsy showing wide fibrotic band separating regenerated nodules—postnecrotic cirrhosis.

was palpated 4 cm. below the right costal margin and the tip of the spleen was felt. Laboratory studies were indeterminate. Surgical exploration was considered preferable to needle biopsy of the liver. The biliary tree appeared normal, as was the result of the operative cholangiogram. Needle biopsy of the liver revealed typical cholangiolitic hepatitis.

The postoperative course was progressively downhill, complicated by development of pseudomembranous enterocolitis due to *Staphylococcus aureus*. Death occurred on March 7, 1959, following hepatic coma for approximately 4 days. Sections of the liver revealed progression of the previously diagnosed lesion with considerable hepatocellular necrosis, bile staining, and thrombosis with bile duct proliferation. In addition, bilateral staphylococcal renal cortical abscesses were found at necropsy.

This case illustrates a severe type of cholestatic or cholangiolitic hepatitis with death unquestionably hastened by surgical intervention, if not solely caused by it.

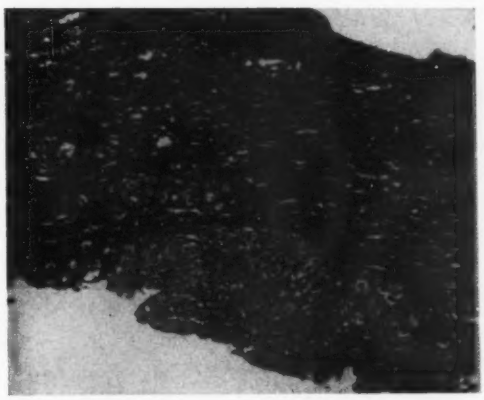
Case 5. A 51 year old white man was admitted to the hospital on May 25, 1956, with pyloric obstruction and gastrointestinal bleeding. Two thousand cubic centimeters of whole blood was administered, and on May 29 subtotal gastric resection was performed for a penetrating duodenal ulcer. The liver was normal except for a small subhepatic abscess, which was drained. Two additional liters of blood were given during operation. The postoperative course was uneventful, and 3½ months later the patient was well.

However, in October 1956, he noted insidious onset of anorexia, jaundice, and itching. Despite prompt treatment and early improvement, relapse occurred, a progressive hepatic lesion developed, and the patient died of massive gastrointestinal bleeding and subsequent hepatic failure in May 1958. Liver biopsy on June 19, 1957, revealed an extremely severe type of postnecrotic cirrhosis (Fig. 4).

This case illustrates the tragedy which homologous serum jaundice may represent when a patient survives a major surgical procedure only to fall prey to progressive homologous serum jaundice as a result of blood transfusions at operation.

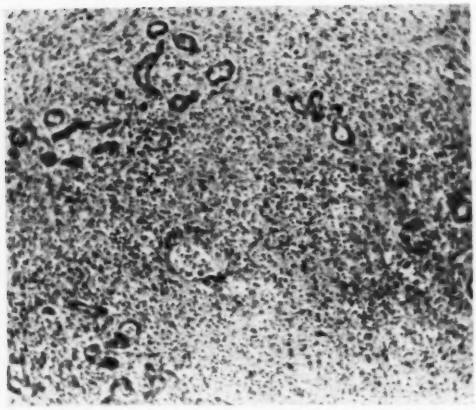
Case 6. A 54 year old white man was admitted to the hospital on Feb. 12, 1951, with acute, diffuse abdominal tenderness, fever, diarrhea, and dehydration. On the 16th hospital day evidence of pneumonia, pulmonary congestion, and heart failure developed, with increasing fever and toxicity, along with manifestations indicative of a surgical abdominal emergency. Exploratory laparotomy on March 2 revealed acute diverticulitis with sigmoid obstruction. During transverse colostomy blood transfusions were administered. The postoperative course was extremely stormy, but the patient gradually improved until 5 weeks postoperatively, when jaundice developed, with rapid worsening of his condition, and death 5 days later. Necropsy revealed an extremely small, shrunken liver weighing 950 Gm. with microscopic evidence of massive necrosis and collapse (Fig. 5).

FIG. 4



(Case 5) Biopsy (trichrome stain) showing dense fibrous tissue with islands of regenerating hepatic cells.

FIG. 5



(Case 6) Photomicrograph of specimen of liver obtained at necropsy showing complete hepatocellular necrosis with residual stroma and bile ducts.

This case illustrates the fulminating hepatic necrosis that can occur when a patient with severe or chronic illness contracts complicating viral hepatitis during hospitalization when body defenses are exhausted.

Summary

Review of 207 cases of viral hepatitis encountered in a civilian general hospital during a period of 17 years revealed an unexpectedly high incidence of serious disease. The mortality rate was 9.2 per cent. The incidence of postnecrotic cirrhosis was 17.3% and only two thirds of the group had uncomplicated recoveries. This high incidence of complications is attributed to the more advanced age and the higher incidence of other diseases present in this general hospital population.

References

1. Neefe, J. R.: Viral Hepatitis. In *Diseases of the Liver*. Edited by L. Schiff. Philadelphia, J. B. Lippincott Company, 1956, pp. 302-327.
2. Smetana, H.: Pathology of Hepatitis. In *Diseases of the Liver*. Edited by L. Schiff. Philadelphia, J. B. Lippincott Company, 1956, pp. 258-301.
3. Paul, J. R.: Epidemiology of Infectious Hepatitis. In *Hepatitis Frontiers*. Edited by F. W. Hartmann, G. S. LoGrippo, J. G. Mateer and J. Barron. Boston, Little, Brown & Company, 1957, pp. 183-190.
4. MacDonald, R. A., and Mallory, G. K.: The Natural History of Postnecrotic Cirrhosis, Am. J. Med. 24:334, 1958.
5. Klatskin, G.: Subacute Hepatic Necrosis and Postnecrotic Cirrhosis Due to Anicteric Infections with the Hepatitis Virus, Am. J. Med. 25:333, 1958.
6. Lucke, B.: Pathology of Fatal Epidemic Hepatitis, Am. J. Path. 20:471, 1944.
7. Viswanathan, R.: Certain Epidemiological Features of Infectious Hepatitis During the Delhi Epidemic of 1955-56. In *Hepatitis Frontiers*. Edited by F. W. Hartmann, G. A. LoGrippo, J. G. Mateer and J. Barron. Boston, Little, Brown & Company, 1957, pp. 207-209.
8. Thaler, H., Benda, L., and Rissel, E.: Histologic Changes in Viral Hepatitis Studied by Liver Biopsy, Gastroenterology 33:209, 1957.
9. Kunkel, H., Labby, D., and Hoagland, C.: Chronic Liver Disease Following Infectious Hepatitis; Abnormal Convalescence from Initial Attack, Ann. Int. Med. 27:202, 1947.
10. Cullinan, E. R., King, R. C., and Rivers, J. S.: The Prognosis of Infective Hepatitis, Brit. M. J. 1:1315, 1958.
11. Neefe, J. R., Miller, R. G., and Chornock, F. W.: Homologous Serum Jaundice, Am. J. M. Sc. 207:626, 1944.
12. Eliakim, M., and Rachmilewitz, M.: Cholangiolitic Manifestations in Virus Hepatitis, Gastroenterology 31:369, 1956.
13. Dubin, I. N., Sullivan, B. H., Jr., Legolvan, P. C., and Murphy, L. C.: The Cholestatic Form of Viral Hepatitis. Experiences with Viral Hepatitis at Brooke Army Hospital During the Years 1951 to 1953, Am. J. Med. 29:55, 1960.

Electron Microscopy of the Kidney in Health and Disease*

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Electron microscopy is pushing back the shadowy borders of the histologic structure of the cell. The author reviews what has been learned concerning intracellular changes which accompany renal disease.

THE DEVELOPMENT OF THE ELECTRON MICROSCOPE covers a span of approximately 25 years. There were many technical problems to be solved and only recently has it appeared that this modality will be of value in clinical medicine. The purpose of this paper is to describe the fundamentals of electron microscopy, the basic technics developed in the preparation and examination of biologic specimens, and to summarize the normal and pathologic changes in the kidney known to the clinical urologist as well as others who may be interested in the subject.

Obtaining Tissue for Electron Microscopy

All tissue, including that from the kidney, must be absolutely fresh for electron microscopy. If, for example, the renal pedicle is clamped, cut and ligated, a period of 5 to 15 minutes may elapse before a specimen can be obtained from the removed kidney. During this time autolytic changes have taken place and the specimen is unfit for electron microscopy. Therefore, if tissue is to be removed at operation the specimen should be taken before or immediately after the renal pedicle is clamped, by means of a wedge resection or by employing a Turkel needle. It is also possible to clamp the pedicle and immediately inject the fixative solution by hypodermic needle into the pathologic area. The most common source of material to date, however, has been tissue obtained by translumbar percutaneous punch biopsy of the kidney, employing a Vim-Silverman-Franklin needle. This method was first described by Iversen and Brun in 1951,[1] although Alwall[2] employed the method in 1944. The present-day technic of punch biopsy in the prone position was introduced by Kark and Muehrcke[3] in 1954. A minimum of 5 glomeruli is necessary to make a diagnosis. Adequate tissue is obtained in about 75% of biopsy attempts. I am not unmindful of the danger of hemorrhage from punch biopsy and have had occasion to remove a kidney because of hemorrhage following such biopsy performed during a sympathectomy for malignant hypertension.

Preparation of Kidney Tissue for Electron Microscopy

Following the removal of the tissue from the kidney it is immediately cut into small blocks 1 cu. mm. in size with a razor or, in the case of a punch biopsy, the entire section is utilized. To prevent autolysis the tissue is cut on a piece of dental plate wax in a drop of fixative. The block is then fixed in 1% osmic acid solution buffered with barbital to a pH of 7.35 as described by Palade[4] in 1952. This method gives a minimum of artefacts and has become as standard a method for electron microscopy as formalin has become standard for paraffin sections. The preparation of osmic acid as a fixative is quite important and is sometimes varied for different organs. For the kidney 1 cc. of fixative solution is required for each 0.0284 Gm. of tissue, and the tissue is therefore placed in small vials containing 1 to 2 cc. of fixing solution. The fixing time is one hour, but tissue may be left in the osmic acid solution for 2 hours. During this period the vial is kept in ice at a temperature of 0 to 4° C. If fixed for a longer period it will become hard and brittle. The specimen, because of its small size, must be handled gently with jeweler's tweezers. After fixation in osmic acid the specimen is dehydrated in successive

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solutions of alcohol from 25% alcohol to absolute alcohol, the period of dehydration requiring two and one-half hours. The procedure is done by hand at present, there being no Technicron for this purpose as for paraffin sections.

The difficulties in securing sufficiently thin sections of biologic material for electron microscopy have been overcome by the employment of Plexiglas as an imbedding material. This contribution was made by Newman, Borysko and Swerdlow[5] in 1949. The specimen after dehydration is placed in a solution of equal parts of absolute alcohol and n-butyl methacrylate, otherwise known as Plexiglas. The kidney and other soft specimens are imbedded in pure n-butyl methacrylate. To harden the Plexiglas for other tissues 10 to 20% methyl methacrylate is added as desired, or in some instances pure methyl methacrylate is employed. A specimen may be impregnated with Plexiglas and imbedded in a harder Plexiglas if desired. There are other imbedding agents also in use, such as an epoxy resin known as Araldite.[6]

Plexiglas as obtained commercially contains a solvent; before it can be used for imbedding tissue a quantity is prepared by the addition of bicarbonate and the solution filtered. After preparation a quantity can be stored in the refrigerator at its usual temperature of 40° F.; refrigeration prevents polymerization and the Plexiglas therefore retains its liquid state until ready for use.

The imbedding of the specimen may be conveniently done by placing the block of tissue in a #2 (or 5 grain) gelatin capsule. To prevent air bubbles 2 drops of the prepared Plexiglas are placed in the bottom of the capsule. This is then placed in the oven for 1 hour at 50° C. until polymerized. It can also be hardened by allowing it to stand at room temperature for 24 to 48 hours, or by exposure to ultraviolet light. The capsule is maintained upright by placing it in a board containing drilled holes of suitable size. In practice large numbers of these capsules are prepared at one time. The block of tissue is then transferred from the half-and-half Plexiglas and alcohol solution to the capsule which is then filled with Plexiglas with a dropper and the top of the capsule replaced. It is again heated to 50° C. for one hour until the Plexiglas hardens. The gelatin capsule is then dissolved in warm water, the Plexiglas block is trimmed into a four-sided prism and is ready for mounting and cutting. The area to be cut should be reduced to a 2 mm. block.

The cutting of the block of tissue for electron microscopy requires a special microtome and much time and effort have been expended on the development of suitable microtomes. While good paraffin sections are 5 or 6 micra in thickness, sections for the electron microscope are in the nature of 50 (500 angstrom units) to 500 millimicra and are therefore only 1/100 as thick as good paraffin sections. Newer microtomes will cut a section 100 A (10 millimicra) in thickness. Such a microtome is sensitive to vibration and temperature changes and must be mounted on a vibration free support in a room of constant temperature. Usually such work is done in the basement of laboratory buildings. Plate glass or diamond knives are used. All cutting is done under binocular stereo-microscopic vision using a heat-free source of illumination at a rate of approximately 20 cuts per minute. The ribbon-like specimen is floated into a pan containing acetone and water attached to the glass knife. The thickness of the specimen is estimated by the color of the specimen on a scale devised by Peachey for this purpose.[7] Periodically thick sections suitable for the light microscope may be taken for the purpose of orientation. Some microtomes are of the mechanical type while others employ a thermal advance mechanism. In the latter type the rod regulating the cut by the glass knife is heated, producing a calibrated expansion of the rod and regulating the size of the cut.

The mounting of the section is done on special round copper supporting grids with a mesh of 100 to 200 to the inch, and each 1.5 mm. in diameter. These grids are coated with a film of Formvar, collodion, or carbon, so the section will stick to the grid. Carbon films are preferable because plastic films have a tendency to drift in the electron beam.[8] The section is transferred to the grid by sliding the grid under the section in the water-acetone bath, using a pair of jeweler's tweezers. The specimen is allowed to dry and is ready for electron microscope examination in 5 to 10 minutes, or the specimen may be stored in a dust-free dry place such as in a Petri dish and examined later.

The section may be stained to increase the

electron density of structures. While the original specimens may be stained before imbedding, staining is usually done after the cutting and mounting of the sections. The section mounted on the copper grid is floated face down in the staining solution. The staining solutions include uranyl acetate, lead acetate, ammonium molybdate, phosphtotungstic acid and sodium urinate. Uranyl acetate is commonly used for staining kidney specimens.

Thick sections for light microscopy may be made for comparative study and are mounted on glass slides. The glass slide is coated with the usual albumin-glycerin mixture ordinarily used for mounting all pathologic specimens. The slide is then covered with 10% acetone water solution and the Plexiglas imbedded specimen transferred to the slide, the excess solution is removed, and the section fixed with heat. The methacrylate is removed by toluene for 5 minutes which is drained off and the process repeated. Sections imbedded in Plexiglas may be stained by hematoxylin and eosin but this cannot be done with epoxy resins (Araldite).

The Electron Microscope

Inasmuch as the electron microscope and its principle of operation is a stranger to most clinicians, I shall describe it briefly to you. Of historical interest may I mention that the emission type of electron microscope producing images of a heated oxide electrode was first made by E. Bruche and H. Johannson in 1932, employing electrostatic lenses and a 300 volt electron beam. The transmission type of electron microscope was suggested by K. Rudenberg in 1931 and such an instrument was described by Ruska in 1934. The first practical instrument was designed by von Borries and Ruska and manufactured by the Siemans Company in Germany in 1939.[9]

The magnification of an electron microscope depends upon the production of an electron beam and the photography of the image produced. Today's electron microscope is capable of magnifying a section from 1,000 to 30,000 times. This magnification can be further increased by enlargement of the photograph to 200,000 to 300,000 times. The maximum theoretical resolution of an electron microscope is 4 angstrom units. It is therefore possible to visualize the structure of tissue at the molecular level. For example the DNA. molecule (desoxyribonucleic acid) is 20 angstrom units in width and 38 angstroms for each complete turn of the double helix. Most electron microscopes have a resolution of 20 angstrom units but recent instruments have a resolution of 10 angstrom units. The power of resolution is more important in microscopy than magnification; by comparison the power of resolution of a light microscope is 2,000 angstrom units. To dramatize the power of the electron microscope we can say that a low-power view of a section by light microscopy compared with an electron microscope photograph holds the same ratio of power as the gross examination of a specimen holds to a low-power study of the section with a light microscope. Some eight companies in the world manufacture electron microscopes today. Most of the electron microscopes in the world are in the United States, although there are probably less than 1,000 electron microscopes in use in the country in industrial and biologic research. In this country the RCA and Norelco-Phillips electron microscopes are in common use mainly because service is an important item.

An electron microscope may be compared with a light microscope that has been turned upside down. To function properly the entire system is pumped free of air; vacuum pumps are an integral part of the electron microscope. Instead of a source of light entering the microscope from below, an electron beam enters the electron microscope from above. The electron beam is produced by heating a tungsten filament surrounded by an electromagnetic field of 50,000 volts stepped up from a line voltage of 440 volts. The small size of the electron makes possible the fine resolution in electron microscopy; each electron is equal to 1/1800 the diameter of a hydrogen atom. The speed of the electron beam produced by the heating of the tungsten filament is increased by passing it through a bank of solenoids after which the electron beam passes through the condenser. The function of the condenser is similar to that in light microscopy, its purpose being to concentrate the beam on the specimen. Instead of a lens, however, an electron condenser consists of a core of soft iron surrounded by a coil of wire producing a magnetic field. An electron beam in a magnetic field is deflected similar to a light beam through a lens, and is focused by means of mechanical adjustment. The biologic speci-

men mounted on the copper mesh grid is placed in a container below the electron condenser through a port which is then closed and air evacuated until a near vacuum is produced. The image is magnified first by an objective electron lens as in light microscopy, and then by a second ocular electron lens system as in light microscopy. In electron microscopy each of these lenses consists of a soft iron core surrounded by fine wire to produce an electromagnetic field. In electron microscopy most of the magnification is done by the ocular system. The image is made visible on a fluorescent screen 20 by 20 cm. in diameter. A binocular microscope is used for closer study of the image. In practice the electron microscope is first focused at a lowered magnification, as in light microscopy, and then the magnification increased. The fluorescent screen is replaced by a spectroscopic glass plate and the photograph taken. Each glass photographic plate will make 5 photographs 10 by 10 cm. in diameter. These can be developed in a few minutes and contact prints or enlargements made for easier study. The enlargement adds only to the magnification but not to the degree of resolution. Stereoscopic images can be taken by tilting the specimen.

Electron Microscopy of a Typical Cell

Electron microscopy consists of a study of the photographs that have been taken and the enlargements that have been made. The examiner must become oriented to the fact that he is studying only a portion of a glomerulus or a portion of a tubule, and that he can study the finer structure and individual components of any given cell. Much of the finer structure of cells in general has been determined by electron microscopy. The majority of the 100 trillion cells of the human body contain a nucleus, cytoplasm and cytoplasmic structures. By electron microscopy it is seen that the typical cell nucleus contains continuous thread-like chromosomes which during the resting stage are twisted and intermingled. These chromosomes become longitudinally double preceding the next cell division. The typical nucleus also contains one or more nucleoli but bodies have also been noted within the nucleoli. Each nucleolus is attached to a specific region of a chromosome; this area has been termed the organizer of the nucleus although all the material in the nucleolus is not necessarily derived from the specific chromosome to which it is attached. Cytochemical studies of the nucleus can be used to show its chemical composition. By electron microscopy the nuclear membrane has been shown to be a double membrane which is fenestrated with precisely centered hexagonal pores and that material can pass from the cytoplasm into the nucleus and vice versa. The nuclear membrane of a cell under the electron microscope was particularly well demonstrated in the ameba proteus by Pappas.

The cytoplasm is composed of a cytoplasmic matrix of a gelled consistency through which course fine fibrillae surrounded by a cell membrane. These fine fibrillae, also termed endoplasmic reticulum, form a lacy network of vesiculated strands but this is not found in the periphery of the cell which is designated as ectoplasm. In some cells the endoplasmic reticulum is irregular but in secreting cells the endoplasmic reticulum is arranged into well-defined canaliculi and can be well demonstrated by the electron microscope. The canaliculi are well illustrated in the pancreatic cell of a guinea pig as shown by Palade and are arranged concentrically about the nucleus. The space between the nuclear membrane is continuous with that of the canaliculi. It is assumed that this system of canaliculi is a means of the transportation of water or various other substances as well as enzymes. Including the endoplasmic reticulum a typical cell contains 10 well-defined structures in the cytoplasm—it contains mitochondria, the Golgi complex, a cell center or centrosome, vacuoles, secretion granules, glycogen granules, pigment granules, and fat droplets. Mitochondria are the power house of the cell and consist of many enzyme systems. They vary in size and shape both according to species as well as the organ. Mitochondria are more numerous in some tissues than in others and are especially numerous in the renal tubules. Mitochondria are in constant motion within the cell. They may divide or fuse with other mitochondria within the cell. They are 0.5 to 1 micron in diameter and under the electron microscope can be seen to be enveloped in a double membrane, the inner layer of which is developed into a series of ridges. The matrix of a mitochondrium is without form but dense granules may be found on occasion. Each mitochondrium contains at least 25 enzymal systems such as the fatty acid-oxidase system,

the cytochrome-linked system and the Krebs cycle. The Golgi complex is associated with the endoplasmic reticulum and consists of lobed and laminated bodies and is most clearly seen near the cell nucleus. It can be shown by silver staining and by osmium tetroxide. The Golgi complex is particularly well developed in nerve cells but it is also well developed in secretory cells. Droplets of fat may also be found in the cytoplasm of cells as well as vacuoles. Granular structures within the cytoplasm may consist of glycogen, secretion granules or pigment granules. The cell center or centrosome is located in the center of the apical region of the cytoplasm. In each centrosome there is a pair (and sometimes more) centrioles usually situated in the center of the centrosome. These are deep staining rod-shaped granules about 0.2 micra in length. Centrioles are closely related to the basal bodies of cilia or flagella, or to a brush border as in the proximal tubule of the kidney. A centriole has 9 circumferential fibrils while a basal body has 9 pairs of fibrils. The cell membrane is an osmotic membrane composed of lipoids and fibrous protein approximating 200 angstrom units in thickness. The cell membrane contains many folds which interdigitate with the adjoining cell.

Electron Microscopy of the Normal Renal Glomerulus

Much of the early electron microscopy of the kidney was done on experimental animals because of the ease of obtaining fresh tissue. The study of the human kidney is relatively recent and practically no studies were made before 1957. Electron microscopy has extended our knowledge of histology, and pathology of the kidney considerably and is an increasingly useful tool in studies of renal physiology and pathologic physiology. To date electron microscopy of the kidney has been largely a research project. How useful electron microscopy will become may depend upon the clinician who may be able to think of practical applications of this modality, and who because of his constant association with patients can obtain human tissue for study.

Electron Microscopy of the Glomerulus in Disease

Electron microscopy has extended our knowledge of diseases involving the glomerulus and sections have been made in adult lipoid nephrosis, childhood nephrosis, acute glomerulonephritis, chronic glomerulonephritis, mixed nephrosis-nephritis, nephritis in lupus erythematosis, diabetic glomerulosclerosis (Kimmelstiel-Wilson disease), preeclampsia and eclampsia, chemical nephrosis, and the kidney in hypertension. The characteristics of these diseases as identified by the electron microscope will be briefly summarized.

(A) *Adult nephrosis.* Nephrosis and the nephrotic syndrome have generally been attributed to disease of the renal tubules but electron microscopy has shown definite changes in the glomerulus, and it is probable that the fundamental cause of the disease is in the glomerulus, the tubular changes being secondary. The recognition of the change is indicated by the use of the term membranous glomerulonephritis by some investigators, or the paranephritic nephrotic syndrome by others instead of the time honored term of lipoid nephrosis. In nephrosis the characteristics by electron microscopy are: (a) loss of pedicles (foot processes) of the podocytes; (b) vacuoles in the cytoplasm of the epithelial cells; (c) swelling of the endothelial cytoplasm; (d) an irregular ruffled contour of the basement membrane in adults; and (e) thickening of the basement membrane occurs on the epithelial side with formation of a new layer containing vacuoles. The effectiveness of therapy can be studied by repeated renal biopsies if desired.

(B) *Childhood nephrosis.* In childhood nephrosis the electron microscopic characteristics are: (a) a loss of foot processes of the podocytes as occurs in the adult,—the more severe the proteinuria the more extensive is the damage to the foot processes; (b) an irregular nodular thickening of the basement membrane; (c) an increase in the number of endothelial cells; (d) deposition of basement membrane-like material between the endothelial cells until the glomerulus is obliterated; and (e) the thickening of the basement membrane occurs on the endothelial side of the basement membrane in childhood nephrosis as compared with the epithelial side in the adult.

(C) *Acute glomerulonephritis.* The glomerulus appears extremely congested. By electron microscopy there is: (a) marked swelling of the cytoplasm of both epithelial and endothelial cells; (b) the hypercellularity is seen to be the result of proliferation of the endothelial capillary cells; (c) between the endothelial cells is a deposition of basement

membrane-like material; and (d) it is interesting to note that the foot processes maintain their identity even in the most severe infection.

(D) *Chronic glomerulonephritis.* By electron microscopy there: (a) is a marked increase in the number of endothelial cells; (b) these are surrounded by basement membrane-like material called hyaline until the glomerulus is partially or completely obliterated; and (c) it is seen the the foot processes maintain their identity even in the presence of severe glomerular disease.

(E) *Nephrosis-Nephritis.* Patients with nephrosis who later develop nephritis, or patients with chronic glomerulonephritis who develop a nephrosis syndrome, show: (a) a loss of foot process; (b) mild proliferation of the endothelial cells; (c) thickening of the basement membrane; and (d) deposition of basement membrane-like material between the cells until the glomerulus is largely obliterated.

(F) *Lupus erythematosis* (L.E. kidney). The characteristic changes seen in the kidney are pathognomonic of the disease. (a) By electron microscopy it is seen that the wire loop lesion in the glomerulus is the result of fibrinoid deposition (an exudative process) on the endothelial surface of the basement membrane. The wire loop lesion is a late manifestation of the disease. Fibrinoid deposition occurs in the endothelial wall of the capillary and can be seen in early lesions. (b) Thickening of the basement membrane and (c) loss of foot processes are a part of the pathologic process in the L.E. kidney.

(G) *Diabetic glomerulosclerosis* (Kimmelstiel-Wilson disease). By light microscopy a diffuse and nodular type have been differentiated. The glomerular changes occurring in long-standing diabetes by electron microscopy show: (a) thickening of the basement membrane which may be 2 to 5 times normal; and (b) that the hyaline deposit is located between the endothelial cells of the glomerular capillary but outside the cytoplasm of these cells. The location of the deposit is similar to that of chronic glomerulonephritis. The material is similar to that of the basement membrane and eventually surrounds the endothelial cells. (c) In later stages the hyaline becomes vacuolated. (d) Foot processes are present in diabetic glomerulosclerosis.

(H) *Amyloid nephrosis.* By light microscopy amyloid appears to involve the glomerulus diffusely, but by electron microscopy, (a) the deposit is seen to be located in the basement membrane producing marked thickening; (b) the deposit on electron microscopy is lighter than that of normal basement membrane and has a foamy appearance; and (c) foot processes are present unless the disease is complicated by a lipoid nephrosis.

(I) *Preeclampsia and eclampsia.* The bloodless appearance of the glomerulus by light microscopy is seen by electron microscopy to be the result of: (a) marked swelling of the endothelial cytoplasm; (b) the basement membrane is not thickened; (c) in some instances fibrinoid material is deposited between the endothelial cells and between the endothelium and the basement membrane; (d) the foot processes are present and appear normal; and (e) in some instances the cytoplasm of the epithelial cells is increased.

(J) *Chemical nephrosis.* The effect of drugs on the glomerulus may be illustrated by the effect produced by the long-continued administration of trimethadione (Tridione) used in epilepsy as in a case described by Maultner.[11] (a) The basement membrane is increased in thickness, and (b) some foot processes become fused and form a scalloped edge.

(K) *Bilateral renal vein thrombosis.* In an 18 day old infant with bilateral renal vein thrombosis, the only change noted was that the foot processes of the glomerular epithelial cells were replaced by sheets of cytoplasm.

(L) *Hypertension.* Hypertension produced experimentally by choline deficiency in rats shows: (a) a thickening of the pedicles, with (b) a narrowing of the spaces between them, and (c) that the basement membrane is thicker than that normally seen. Similar findings may be expected in hypertension in man and perhaps variations occur depending upon the etiologic factor.

Electron Microscopy of the Normal Renal Tubules

Electron microscopy of the renal tubules can be expected to extend further our knowledge of histology and pathology of the kidney, and our knowledge of renal physiology. To date, however, only scattered information is available on the human kidney and the only detailed studies of the entire nephron have been made on the tubules of the mouse and rat.

In the proximal portion of the proximal convoluted tubule the lumen is generally

found to be collapsed. A magnification of 10,600 times will show the nucleus with a nucleolus and the well-developed brush border and numerous mitochondria. At a higher magnification of 32,000 times the brush border will be seen to be opposed to tubular invaginations of the cytoplasm. The finer structures of the mitochondria will be seen to consist of a triple layer outer wall and triple layered membranes within the mitochondria. In addition microbodies *(mb)* will be seen which have no definite structure and may be young mitochondria. The cell will also be seen to contain lipids *(d)*, the Golgi complex close to the nucleus *(G)*, basement membrane *(E)*, double cell borders *(cm)*, vacuoles *(v)*, while the cell substance consists of a hyaline matrix. The large number of mitochondria will be consistent with the heavy functional load of the proximal tubules and includes both the reabsorption of water and electrolytes as well as secretion of various substances. By ultracentrifuging it has been determined that the enzyme molecules are located in the membranous structures within the mitochondria.

The distal portion of the proximal convoluted tubules will show the following: (a) the tubules will not be collapsed like the proximal portion; and (b) the brush border will be well developed and regular if shown at a magnification of 43,200. (c) By histochemical studies the brush border will be shown to be very rich in the enzymes alkaline phosphatase which is intimately connected with reabsorption of glucose. (d) The mitochondria will be smaller, more round, and more irregular in their location than in the proximal portion. (e) The distal portion of the proximal convoluted tubules will contain vacuoles, but (f) there is no infolding of the cell membrane between the brush border, as in the proximal portion less free flow of fluid can be expected.

Of interest is the relationship of the peritubular capillary walls to the renal tubule. Upon magnification of the capillary and its basement membrane, there will be a layer of cement substance between the endothelium and the basement membrane. The endothelial sheet will be fenestrated. The multitude of ribonucleic acid granules characteristic of the proximal convoluted tubules will be seen, as well as the infolding of the cytoplasmic membrane. Fenestrations in the peritubular capillary wall will be found to measure .06 Å.

In the thin segment of the loop of Henle at 13,600 magnifications, (a) the central lumen will be seen to be patent; (b) the cytoplasm of the cell will be attenuated; and a nucleus with its nucleolus *(n);* (c) the mitochondria will be few and very small; (d) there will be few microvilli; (e) the basement membrane will be well defined; and (f) as the ascending loop of Henle approaches its own glomerulus it will increase in thickness.

The distal convoluted tubule contains cells that are columnar in type and the electron microscope will reveal the following: (a) the mitochondria will be seen to be arranged in palisades,—they are long and dense, closely packed together; (b) the lamellae of the mitochondria will be either oblique or longitudinal and not transverse as in the proximal convoluted tubule; (c) the cytoplasm will be arranged in longitudinal canaliculi which surround each mitochondrium; (d) the cytoplasm will be lighter in color than in the proximal tubule and contain vacuoles; (e) the nucleus will be in the apical portion of the cell; (f) the basement membrane will be thin and homogenous in appearance; (g) the brush border will be absent and represented by a few microvilli; and (h) there will be also vesicles in the cytoplasm indicating a secretory process or the formation of ammonia or the adjustment of the pH of the urine.

The collecting tubules consist of cuboidal epithelium with a patent lumen. Under the electron microscope most cells will be seen to have: (a) a light cytoplasm but interspersed between them will be a few cells with dark cytoplasm; (b) in both types of cells the mitochondria will be few and spherical or spheroid in shape; (c) the surface will show a few microvilli *(mv)* the border between a light cell *(L)* and a dark cell *(D)* will be seen; (d) the dark cell will have more vesicles *(V)* in the cytoplasm of the cell apex, and more microvilli (mv) and more mitochondria than in the light cell. It is presumed therefore that the collecting tubules also take part both in absorption and secretion. (e) It has been shown experimentally that the number of dark cells can be increased by hypopotassemia.

Electron Microscopy of the Renal Tubules in Disease

The renal tubules like the glomerulus reveal pathologic changes under the electron microscope not seen by the light microscope. In adult lipoid nephrosis the proximal convo-

luted tubule will show: (a) a diminution in height or complete loss of the brush border; (b) only remnants of mitochondria will be seen; (c) there will be many granules probably of mitochondrial origin; (d) the basement membrane will be moth-eaten; (e) there will be many vacuoles; and (f) the cytoplasm of one cell will be bulging into the lumen and will shortly be extruded. This change appears even more marked in childhood nephrosis and only remnants of mitrochondria can be seen. The loop of Henle in lipoid nephrosis in a child shows: (a) swelling of the epithelial cytoplasm which bulges into the lumen of the tubules, and (b) the collecting tubules show a thickening of the basement membrane.

The proximal convoluted tubule in diabetes shows a thickening of the basement membrane which consists of a large number of parallel lamellae.

Some information regarding kidney stone formation has been gained from the electron microscope. Stones may be produced by the administration of parathyroid hormone or by the administration of large doses of vitamin D. The number of mitochondria is decreased with an increase in the number of microbodies and is considered to be a sign of tubular degeneration. When these experiments are continued the microbodies increase in size and develop increased electron density; globules of lesser electron density appear in the cell which increase in size until the cell ruptures. This less electron dense material fills the entire lumen of the tubule and corresponds to the hyaline material seen by light microscopy. It is probable that the precipitation of calcium salts occurs on this hyaline matrix in the tubular lumen. These plates of calcium have been measured and found to be 50 by 200 A^{12} to 300 A^{13} units in size and correspond to the usual size of apatite crystals.

The electron microscope has also increased our knowledge of renal tumors. Recent studies have proved the fact that hypernephromas are of tubular cell origin. Electron microscopic studies show that such tumors contain a nucleus relatively unchanged containing fine chromatin and a nucleolus. The cytoplasm presents three characteristic changes. These changes consist of: (a) a marked increase in the number of mitochondria; (b) deposits of fat; and (c) deposits of glycogen. The enlarged mitochondria have a decreased electron density and are often pushed tightly against each other. The internal architecture of the mitochondria is deranged, and the internal membranes are often incomplete and sometimes fused. There is also an increase in the number of microbodies containing a finely granular matrix. Between the mitochondria there are fat deposits of increased electron density. These vary in size and may fuse to form large masses. The cell in hypernephroma is also abundant in glycogen which occurs as plaques of poor electron density. The substance is finely granular—forming a fine reticulum throughout the cell. At a higher magnification the basement membrane is shown to have well-developed intracytoplasmic lamellae, therefore demonstrating the tubular origin of hypernephroma.

In conclusion, I would like to emphasize that the preliminary groundwork for electron microscopy has been completed and that though my thoughts may be premature, I believe the clinical urologist should acquaint himself with the subject sufficiently so he may contribute his practical knowledge as well as clinical material to further advance our knowledge of the kidney.

References

1. Iversen, R. M., and Brun, C.: Aspiration Biopsy of the Kidney, Am. J. Med. 11:324, 1951.
2. Alwall, N.: Aspiration Biopsy of the Kidney, Acta med. scandinav. 143:430, 1952.
3. Kark, R. M., and Muercke, R. C.: Biopsy of the Kidney in the Prone Position, Lancet 1:1047, 1954.
4. Palade, G. E.: A Study of Fixation for Electron Microscopy, J. Exper. Med. 95:285, 1952.
5. Newman, S. B., Borysko, E., and Swerdlow, M.: New Sectioning Technique for Light and Electron Microscopy, Science 66:110, 1949.
6. Glauert, A. M., Rogers, G. E., and Glauert, R. H.: A New Embedding Medium for Electron Microscopy, Nature, London, 178:803, 1956.
7. Peachey, L. D.: Thin Sections. I. A Study of Section Thickness and Physical Distortion Produced during Microtomy, J. Biophys. & Biochem. Cytol. 4:233, 1958.
8. Watson, M. L.: The Use of Carbon Films to Support Tissue Sections for Electron Microscopy, J. Biophys. & Biochem. Cytol. 1:183, 1955.
9. Encyclopaedia Britannica.
10. Rhodin, J.: Electron Microscopy of the Glomerular Capillary Wall, Exp. Cell Res. 8:572, 1955.
11. Tenth Annual Conference on the Nephrotic Syndrome. J. Metcoff, National Kidney Disease Foundation, New York, 1959.
12. Scarpelli, D. G., Tremblay, G., and Pearse, A. G. E.: A Comparative Cytochemical and Cytologic Study of Vitamin D Induced Nephrocalcinosis, Am. J. Path. 36:331, 1960.
13. Engfeldt, B., Gardell, S., Hellstrom, J., Iremark, B., Rhodin, J., and Strandh, J.: Effect of Experimentally Induced Hyperparathyroidism on Renal Function and Structure, Acta endocrinol. 29:15, 1958.
14. Tenth Annual Conference on the Nephrotic Syndrome. J. Metcoff, National Kidney Disease Foundation, New York, 1959.

Because of the limits imposed on the reference list, the author will supply further references for collateral reading upon request.

Etiology and Therapy of Diabetic Retinopathy: A New Approach*

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It has become quite evident that the vascular lesions and complications of diabetes mellitus are not dependent upon glucose levels in the blood. Other biochemical substances are related to these abnormalities though their exact role has not been clearly defined.

FOR A LONG TIME following the discovery of insulin it was believed that a sufficient supply of this hormone would completely correct all the metabolic defects of diabetes mellitus. This concept was both logical and scientific and stood a long test of time because it reputedly reduced complications and prevented an early death from acidosis. The acidotic death has indeed been prevented and exogenous insulin had been the agency of longer life to 3 generations of diabetic patients. Unfortunately, however, the passage of time and the accumulation of experience has granted realization that insulin lack is not the sole therapeutic determinant of this disease. The continued observation of patients who have survived on insulin has gradually aroused awareness of the universality of the complications which evolve concomitantly with the continuation of the diabetic complex. Foremost among the complications are those which effect the smaller blood vessels producing a pathologic metamorphosis which especially endures as the clinical entities of diabetic retinosis and Kimmelstiel-Wilson disease.

The inferential consequence of increased awareness of the failure to control diabetic complications through insulin has led to consideration of metabolic defects of diabetes other than that of glucose. Such consideration, however, must of necessity be contingent upon the concept that a diabetic metabolic defect exists which is not reduced through adequate insulin supply. The emergence of such a concept has been retarded through compliance, over long years, by a large segment of the profession with the acceptance of the orthodox belief in insulin as the answer to all phases of disease in the diabetic.

In the pre-insulin era a large fund of knowledge had already been accumulated concerning the disorders of fat metabolism which occurred secondarily to the failure of glucose utilization. These disorders have been well known and many investigations, continuing to the present, have expanded and elucidated the mechanisms involved. Consequently, we now know that inability of glucose to pass the cell membrane results in failure of lipogenesis which in turn leads to an outpouring of fatty acids into the blood stream with resulting hyperlipemia and eventual ketosis. The known quadri of fat disorders in diabetes mellitus are those of synthesis, storage, utilization and transport, and they are all intimately related with failure of glucose to pass the cell membrane. For this latter reason these fat disorders are considered to attain normalcy in the adequately controlled diabetic. This postulate is based upon inadequate methods of blood fat determination and in many instances the determination of cholesterol alone was used as the index of other serum lipid levels. The use of serum cholesterol levels as an index of the level of other fractions of blood lipid is a pure assumption and has no basis in fact, and wide divergence of the triglyceride and cholesterol fractions occurs frequently.

In states of inadequate utilization of glucose two principal changes occur to the serum lipids, consisting of elevation in the triglyceride and unesterfied fatty acid fractions. The triglyceride fraction can increase to extreme levels which causes lactescence of the serum and eventual formation of ketone bodies. With measures directed toward greater glucose utilization and metabolic stabilization,

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the serum triglycerides revert in the direction of normalcy which state, however, they fail to completely attain. This means that serum triglycerides are constantly elevated in the diabetic state regardless of glucose control and implies the presence of a metabolic defect of fats which is independent of insulin adequacy and which is probably primary in character.

This disorder of fat metabolism is relevant to all of the known derangements of this entity in diabetes but is particularly related to transport, which medium allows for the quickest and simplest study method of the problem. The triglycerides of blood serum are present in colloidal suspension as discreet particles measuring 0.5 to 1 micron and less, which are in rapid brownian movement and called chylomicrons. These blood particles consist of about 80% triglycerides, with the remainder consisting of cholesterol, phospholipids and protein.[1] Chylomicrons have been extensively studied by Gage and Fish,[2] who first named them, and by Frazer,[3] Moreton[4] and many others. They are very well and easily visualized by the darkfield microscope where they appear as white, discreet dancing particles in continuous movement. The number of particles in a given high power field can be counted or determined by several methods, all of which afford varying degrees of accuracy.[3-6] Nevertheless, a distinct parallel between serum chylomicrons and triglyceride levels has been demonstrated, which indicates that determination of serum levels of chylomicrons is a satisfactory reflection of the level of triglycerides.[3,7]

This method of triglyceride determination has been used by me in about 200 diabetic patients of whom approximately 20% were considered to be under good glucose control. In all patients the fasting serum levels of chylomicrons were above normal thus indicating a hyperlipemia of triglycerides and demonstrating the disorder of fat transport in diabetes which is independent of insulin. This observation is substantiated by the studies of Adlersberg[8] whose investigations in diabetic patients revealed the constant elevation of the triglyceride fraction and also by Bierman[9] who demonstrated an elevation of nonesterfied fatty acids in controlled as well as uncontrolled diabetes.

In addition to the derangement of fat transport another metabolic disorder occurs in diabetes which is not correctable by insulin. Increasing evidence is appearing in the literature which tends to show that a gross disturbance of the metabolism of mucopolysaccharides, the amorphous components of ground substance, also occurs.[10-12] This appears evident in the histochemical changes which occur in the retina, kidney and pancreas. The obvious changes which are seen consist of an overproduction of hyaline material in which small droplets of lipid substances are dispersed. These things are evident in the retinal microaneurysms, the intercapillary glomerular lesions and in the pancreatic islets. These changes are obviously associated with the severe functional failure of late diabetes and are intimately related to the smaller blood vessels. The striking simultaneity of lipids and excessive ground substance in these lesions is very likely not merely fortuitous, but perhaps indicates a causal relation. This interesting concept has been furthered by the studies of Hartroft[13] and also of Pope,[14] who have made very significant contributions to this subject. Additional confirmatory studies reported in the literature point to the idea that the disastrous final vascular lesions of diabetes occur as a result of the disorders of fat transport.[15-17] This conclusion is of necessity circumspect and requires considerable additional elucidation to be established. This latter caution, however, does not preclude consideration of empirical therapeutic efforts based upon the hypothetical concept that a long interval of hyperlipemia of triglycerides in diabetes results in the characteristic disorder of polysaccharide metabolism. Efforts directed toward the reduction of hyperlipemia can be fruitful through the conjoined actions of sustained control of blood glucose and the operation of clearing agents for serum triglyceride. I have implemented this proposition in 5 patients with diabetic retinopathy for one and a half years using 1,500 international units of potassium heparin by the sublingual route 4 times daily. This therapeutic procedure has resulted in a reduction of fasting levels of chylomicrons in all patients with an accompanying partial regression of the retinal lesions in 4 and a failure to improve in the last. This retrogression, viewed ophthalmoscopically, is unequivocal and involves disappearance of both exudative lesions and microaneurysms. The rate of disappearance is very slow and gradual so several months of therapy

is required before positive evidence of change is noticed.[18] These observations are paralleled by the work of Van Eck[19] who obtained partial clearing of diabetic lesions in individuals upon a very low fat diet for 12 and 18 month periods and who also found reduction of fasting levels of serum triglycerides.

It appears patent that correction of the disorder of fat transport in diabetes mellitus results in an amelioration of the characteristic retinal lesions and there is reason to assume that improvement occurs also in the renal lesions.[20] These investigations and results are most obviously in the preliminary stage, and it is necessary to conclude that considerable further efforts will be required for complete exposition of the problem both from the standpoint of pathogenesis and therapy.

References

1. Havel, R. J., Eder, H. A., and Bragdon, J. H.: Distribution and Chemical Composition of Ultracentrifugally Separated Lipoproteins in Human Serum, J. Clin. Invest. 34:1345, 1955.
2. Gage, S., and Fish, P.: Fat Digestion, Absorption and Assimilation in Man and Animals as Determined by the Darkfield Microscope and a Fat Soluble Dye, Am. J. Anat. 34:1, 1924.
3. Frazer, A. C., and Stewart, H. C.: Ultramicroscopic Particles in Normal Human Blood, J. Physiol. 90:18, 1937.
4. Moreton, J. R.: Physical State of Lipids and Foreign Substances Producing Atherosclerosis, Science 107:371, 1947.
5. Zinn, W. H., and Griffith, G. C.: Study of Serum Fat Globules in Atherosclerotic and Non-atherosclerotic Male Subjects, Am. J. M. Sc. 220:597, 1950.
6. Marder, L., Becker, G. H., Maizel, B., and Necheles, H.: Fat Absorption and Chylomicronemia, Gastroenterology 20:43, 1952.
7. Fourman, L. P. R.: Chylomicron Serum Levels in Tropical Sprue, Tr. Roy. Soc. Trop. Med. & Hyg. 41:537, 1948.
8. Adlersberg, D., and Eisler, L.: Circulating Lipids in Diabetes Mellitus, J.A.M.A. 170:1261, 1959.
9. Bierman, E. L., Dole, V. P., and Roberts, T. N.: An Abnormality of Non-esterfied Fatty Acid Metabolism in Diabetes Mellitus, Diabetes 6:475, 1957.
10. Lerman, S., Pogell, B. M., and Lieb, W.: Serum Proteins and Total Glucosamine in Diabetic Retinopathy and Glomerulosclerosis, A.M.A. Arch. Ophth. 57:354, 1957.
11. Fry, I. K., Trounce, J. R., and Cook, C. A.: Vascular Disease in Diabetes Mellitus: Relation of Raised Blood Protein-bound Hexose Levels, Diabetes 8:174, 1959.
12. Jacobs, H. R.: The Bound Glucosamine of Serum Mucoid in Diabetes Mellitus: Fluctuations Observed Under the Influence of Insulin, J. Lab. & Clin. Med. 54:116, 1949.
13. Hartroft, W. S.: Fat Emboli in Glomerularcapillaries of Choline-deficient Rats and of Patients with Diabetic Glomerulosclerosis, Am. J. Path. 31:381, 1955.
14. Pope, C. H., Jr.: Retinal Capillary Microaneurysms—A Concept of Pathogenesis, Diabetes 9:9, 1960.
15. Faber, M.: The Human Aorta, Arch. Path. 48:342, 1949.
16. Brante, G.: Gargoylism—A Mucopolysaccharidosis, Scandinav. J. Clin. & Lab. Invest. 4:43, 1952.
17. Nikkila, E. A., and Majanen, S.: The Blood Heparinoid Substances in Human Atherosclerosis, Scandinav. J. Clin. & Lab. Invest. 4:204, 1952.
18. Finley, J. K., and Weaver, H. S., Jr.: The Use of Heparin in the Treatment of Diabetic Retinopathy: A Preliminary Report, Am. J. Ophth. 50:483, 1960.
19. Van Eck, W. F.: The Effect of a Low Fat Diet on the Serum Lipids in Diabetes and Its Significance in Diabetic Retinopathy, Am. J. Med. 27:196, 1959.
20. Friedenwald, J. S.: Diabetic Retinopathy, J.A.M.A. 150:969, 1952.

Discussion (Abstract)

Dr. Thomas H. Pettit, St. Louis, Mo. Diabetic retinopathy, its etiology and therapy, is a timely subject since it is a major cause of blindness today, and all too frequently strikes the young diabetic who is just reaching the productive years of life.

In studying diabetic retinopathy, one of the most productive approaches has been to compare diabetics with and without retinopathy. One of the interesting differences noted in these two groups is in the levels of serum lipids.

Thus, it is logical to attempt the use of various lipid clearing agents in this disorder to hope to return the serum lipid levels toward normal. Heparin was demonstrated, in the early 1950's, to be active in clearing certain lipemias presumably by activation of a lipoprotein lipase. The use of heparin in diabetic retinopathy is rational and, in fact, has been used by others. Dr. Finley's approach to the problem with serial chylomicron counts and the use of sublingual heparin seems unique.

We have had some limited experience with the use of parenteral heparin in diabetic retinopathy at Washington University in St. Louis. A group of patients with diabetic retinopathy was divided into a treated and a control group. The treated group received 100 mg. of heparin and multiple B vitamins intramuscularly daily for a period of approximately 2 years, while the control group received no special therapy. Examination for changes in the fundi were made in each group at regular intervals. No discernable difference was demonstrable in the two groups except that, if anything, the controls did slightly better than the treated group. In both groups there were cases which improved and cases which had exacerbations. We thought this merely illustrated the fluctuating course of this disease with remissions and exacerbations. It is this fluctuating course that makes any treatment so difficult to evaluate.

Another problem in therapeutic evaluation in this disease is the fact that there are several stages of diabetic retinopathery:—early, moderately advanced, and advanced—retinitis proliferans and recurrent hemorrhage. It is conceivable that therapy may arrest or reverse the retinopathy at one stage and not at another. Thus, the stage at the time of treatment is relevant. Another approach to the problem in recent years has been the use of low fat diets to lower the blood lipids. Dr. Kempner and his group reported on the use of the rice diet in diabetics with retinopathy, with improvement in 13 of 44 studied. Dr. Finley mentioned the work of Van Eck who reported on the use of a low fat diet (less than 20 gm. per day) in patients with diabetic retinopathy, and demonstrated that his diet effectively lowered the blood lipids and in 8 of 10 there was noted resorption of retinal exudates. However, at the same time 9 of 10 continued to develop the other manifestations of diabetic retinopathy, namely microaneurysms and hemorrhages. Another interesting approach to this problem is suggested by the work of Dr. Seifter and his group. They have demonstrated a lipid mobilizing factor produced by the posterior pituitary which, on injection or secretion, produces lipemia. It may be that the lipemia of diabetes is due to the over-action of this factor. They also point out that this lipemia is not cleared well by heparin but is cleared well by a partially depolymerized hya-

luronic acid. It would be interesting to study this agent in diabetic retinopathy.

In closing, I would like to mention that the problem of diabetic retinopathy appears to be considerably more complex than the lipid disorder we have discussed today. In comparing diabetics with and without retinopathy there have been many other differences noted, such as the blood levels of glucosamine polysaccharides and alpha-2-globulins. There also seem to be differences in the two groups in adrenal pituitary function and the utilization of vitamin B_{12}. It is indeed a complex problem and I am grateful to Dr. Finley for his efforts to unravel it for us and for the opportunity to discuss his paper.

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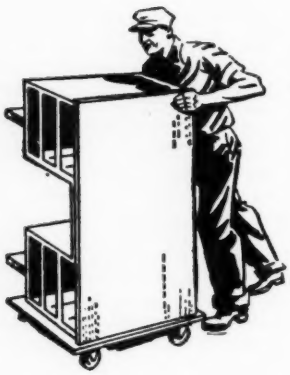

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The Industrial Hygienist's Contributions in the Field of Occupational Health*

ELMER P. WHEELER,† *St. Louis, Mo.*

This specialist has the responsibility of the environment in industrial plants as related to health. Obviously, he and the industrial physician make up a team which is absolutely necessary for the welfare of the worker.

INDUSTRIAL HYGIENE has become a well-established field of specialization in the United States, represented by more than 1,200 scientists and engineers in industry, government, universities, insurance companies and research agencies. We, in this profession, come principally from the basic fields of the physical sciences, such as chemistry and physics, the biologic sciences including biochemistry and physiology, and from practically all of the basic engineering specialties. Our objective is to work in close collaboration with industrial physicians and medical scientists and to share with them a joint responsibility for securing and maintaining the health, productivity and well-being of workers in industry.

Industrial hygiene has been defined as "that science and art devoted to the recognition, evaluation and control of those environmental factors or stresses, arising in or from the work place, which may cause sickness, impaired health and well-being, or significant discomfort and inefficiency among workers or among the citizens of the community."[1] The key words in this definition are "recognition," "evaluation" and "control." The industrial hygienist, because of his training and experience, should be able to:

(A) *recognize* the environmental factors and stresses associated with work and work operations and to understand their potential effect on man;

(B) ***evaluate,*** on the basis of experience and with the aid of quantitative measurement technics, the magnitude of these stresses in terms of the potential to impair man's health and well-being; and

(C) prescribe methods to eliminate, *control* or reduce such stresses when necessary to alleviate their effects.

Recognition of environmental factors and stresses which influence health requires a familiarity with work operations and processes. The factors and stresses most commonly encountered may be categorized as:

1. Chemical, in the form of liquid, dust, fume, mist, vapor or gas;
2. Physical energy, such as electromagnetic and ionizing radiations, noise and vibration and extremes of temperature and pressure;
3. Biologic, such as insects, molds, bacteria and viruses;
4. Ergonomic, such as body position in relation to the task, monotony, boredom, repetitive motion, worry, work pressure and fatigue.

Evaluation of the magnitude of these environmental factors or stresses must be based on a knowledge of whether they are immediately dangerous to life and health, whether they produce an acceleration of the aging process or whether they will cause only significant discomfort and inefficiency. Quantitative measurement allows an estimate as to the healthfulness of the environment, either for short periods or for a lifetime of exposure.

The recommendations for corrective *control* procedures, when necessary to protect health, are based on past experience, knowledge and the quantitative data available. Among control measures most frequently used are:

1. Isolation of a process or work operation to reduce the number of persons exposed;

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2. Substitution of a less harmful material for one which is more dangerous to health;

3. Alteration of a process to minimize human contact;

4. Ventilation and air cleaning to provide an atmosphere safe for human occupancy;

5. Reduction of exposure to radiant energy by shielding, increasing distance and limiting time;

6. Wet methods to reduce emission of dust to the atmosphere such as in mining and quarrying;

7. Good housekeeping, including cleanliness of the work place, proper waste disposal, adequate washing, toilet and restroom facilities, healthful drinking water and eating facilities; and control of insects and rodents;

8. Personal protective devices, such as special clothing and eye and respiratory protective equipment.

Within the broad scope of industrial hygiene, the nonmedical industrial hygienist is responsible for a number of functions which may be described in more definite terms. The hygienist studies work operations and processes obtaining full details of the nature of the work, materials and equipment used, products and by-products, number and sex of employees, and hours of work. In making appropriate measurements to determine the magnitude of exposure or nuisance, he must select and frequently devise methods and instruments suitable for such measurements. Where information on toxicity is not available, he must study and test materials associated with the work operation or process. He may study and test biologic materials such as blood and urine by chemical and physical means, when such examination is appropriate and will aid in determining the extent of exposure. He must interpret the results of the examination of the environment and present specific conclusions to appropriate interested parties such as management and health officials. Based on his interpretation of the results, the industrial hygienist must make specific decisions as to the need, design and effectiveness of control measures. He may participate in the legislative, education, and promotional activities for the prevention of occupational disease. Finally, he may conduct research to advance knowledge concerning the effects of occupational exposures upon health and means of preventing occupational health impairment, community air pollution, noise, nuisance and related problems.

This elaboration may suggest the necessity for encyclopedic knowledge. Such an implication is not intended. Rather, as Professor Theodore Hatch has stated, the industrial hygienist, "without attempting to become a physician or physiologist, must nevertheless acquire an independent capacity to understand and evaluate the human side of the man-environment equation in order most wisely to employ his primary skills in physical science and engineering to 'recognize, evaluate and control' the work environment."[2]

The complexities of the industrial environment today and the potential that this environment may adversely affect health and well-being have led to distinct specialties within the profession of industrial hygiene. For example, in the annual meetings of the American Industrial Hygiene Association, it has become necessary to schedule specific sessions for those interested to the greatest degree in limited areas. Thus, we find scientific and technical programs developed to satisfy those working daily in: (1) toxicology, (2) chemical and analytical technics, (3) radiation, (4) noise control, (5) air pollution, (6) environmental engineering, and (7) human engineering.

It is in these areas of joint interest to the physician and industrial hygienist that the latter have contributed to the promotion of occupational health.

Toxicology. To the nonmedical industrial hygienist, the toxicologist represents the scientist who predicts the effects of chemical contaminant in the environment on those exposed to those contaminants. The predictions are possible only after appropriate, careful and thorough animal research. Based on reasonable extrapolation of the animal data, the predictions are intended to assist the industrial physician in observing and examining the population so that no adverse effects will be undetected even in early stages of development. Primarily, however, the industrial hygienist looks to the nonmedical toxicologist to present him with sufficiently accurate data to establish a guide as to safe levels of the contaminant.

Without a "bench mark"—more properly referred to as maximum allowable concentration, maximum permissible concentration, threshold limit value or hygienic guide—the industrial hygienist must advocate a "zero" level as being the only safe level. Obviously, this solution fails to recognize a dose-response relationship generally accepted by scientists

and may become unduly expensive and restrictive in the development of industrial processes and engineering control. The medical, industrial hygiene, and toxicology literature reflects the mass of data accumulated in the last quarter century by many who classify themselves as "industrial toxicologists" and who would include themselves as "industrial hygienists" rather than research pharmacologists, biochemists or physiologists. Their data, interpretation and advice serve as a foundation for good industrial hygiene practice.

Chemical and Analytical Technics. On several occasions, the speaker has referred to "quantitative evaluation" of the environment. "Qualitative" and "quantitative analysis" brings to every mind the challenging hours spent in a chemical laboratory. Although a well-trained and experienced industrial hygienist may make a fairly accurate estimate of potential exposures in industry on the basis of observation alone, qualitative and quantitative analysis remains as the only accurate evaluation of the environment. As our profession grows, more and more direct reading instruments become available to assist in measurement. With such instruments, individuals with little training or experience can obtain a quantitative answer. The reliability, accuracy, effects of interfering substances and the significance or interpretations of the value obtained limit the usefulness of the instruments in such hands. And even with such instruments, the efforts of the qualified analyst in the development design and methodology incorporated in the instruments are obvious. Perhaps it is unnecessary to point out that the effects of inhaling certain levels of atmospheric contaminants, as employed by the experimental toxicologist in determining toxic effects, could not be measured or predicted without analytical technics to indicate what levels exist during the experiments. The analytical technic developed to establish the atmospheric concentration in the experimental animal chamber for inhalation is commonly the method employed by the industrial hygienist in evaluating the industrial environment.

Radiation. Dr. Quigley has very ably pointed out the problems relating to this area in the previous paper.[3] At this time, mention is only made to the fact that when the atom "became of age," industrial hygienists and industrial physicians, who for many years had been concerned with exposures to x-ray and other radiation sources, formed the nucleus of the "health physics" team which has done such an admirable job in preventing occupational disease in the "atomic industries."

Noise. The last decade has shown an increasing concern for the effects of noise associated with industrial operations. While the industrial physician and his otolaryngological colleague have diagnosed and measured hearing loss due to industrial noise, the industrial hygienist has measured industrial noise levels and contributed in the development and application of acoustical controls.

Air Pollution. Because of the industrial hygienist's interest and concern in the effects and measurement of low concentrations of contaminants in the industrial environment, it is quite natural that many of us today devote equal or more time and effort to considerations of the community atmosphere. Credit for the great advances made to date in cleaning up our cities from the standpoint of heavy smoke, fly-ash and other particulate matter rightfully belongs to mechanical and combustion engineers. With the current popular, political and scientific interest in the more insidious contaminants such as gases, vapors, mists and odors, the use of technics familiar to the industrial hygiene become necessary. The relation of these contaminants to effects on health logically involve the industrial physician and those in occupational health.

Engineering. Perhaps the area of interest to the industrial hygienist least related to the field of medicine is the engineering involved in the elimination or control of occupational health hazards. The list of control measures itemized earlier in this discussion emphasize this point. Among industrial hygienists we find those with undergraduate degrees in electrical, civil, mechanical, chemical, acoustical and sanitary engineering. Additional training and experience has made them expert in the design of processing equipment, process changes, ventilation equipment, air cleaning equipment, instrumentation, etc. Perhaps surprisingly, a number have, through postgraduate training in the biologic sciences, become expert in physiology and respiration, and some, after a few years' experience in the field

of industrial hygiene, have found it desirable to obtain a degree in medicine.

It is hoped that a thread has been woven into this presentation implying an interdependence of the industrial hygienist and those physicians in occupational health. Again referring to a recent paper, Professor Hatch has said:

"No physical measurements of dustiness, of radiation, heat, noise, or light, of chemical fumes or vapors, no matter how precisely these are made, have direct biological meaning but are useful only in proportion to the goodness of their respective calibrations, so to speak, against appropriate biological scales of human health. Thus, standing alone on its foundation of physical science and engineering, industrial hygiene would have little meaning. Through teamwork, however, between the medical scientists and physicians, on the one hand, and the physical scientists and engineers, on the other, it has developed on a strong biophysical base, which provides the link between environment and man. It may be noted here that progress on the medical side is equally limited without such a common base in both the physical and biological sciences. The medical diagnostic techniques, like the physical procedures of the industrial hygienist, when used alone will not tell us that an observed state of ill health was necessarily caused by a particular industrial exposure. Such interpretation is permitted only when the diagnostic findings can be evaluated in relation to quantitative description of the conditions of exposure and both examined in the light of previously established correlations between similar environmental stresses and human response."[4]

References

1. American Industrial Hygiene Association Ad Hoc Comcittee: Industrial Hygiene: Definition, Scope, Function, and Organization, Amer. Indust. Hyg. Ass. J. 20:428, 1959.
2. Hatch, Theodore F.: Training in Industrial Hygiene in the U.S., J. Occup. Med. 2:321, 1960.
3. Quigley, J. A.: Radiation—Industry's Best Understood Problem, South. M. J. (To be published.)
4. Hatch, Theodore F.: *Ibid. reference 2.*

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Management of Late Results in Athletic Injuries to the Knee*

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NO ONE CAN SERIOUSLY DOUBT that the best way to prevent sequelae leading to chronic crippling is to treat the initial injury. In general there has been a great advance in the early treatment of injuries to athletes. This will, in the long run, result in very much less chronic residual disability. However, many are still undertreated. The examples of this are legion. The athletic hero of 45 bragging of the "trick knee" which he has had since high school days is indeed inviting trouble which may well be irremediable due to gross degenerative changes. The great majority of these cases could have been prevented by adequate, early, intelligent treatment recommended by the doctor and accepted by the patient.

The vast majority of injuries to athletes occurs in young, healthy individuals. These youngsters are particularly receptive of the type of definitive treatment which should prevent permanent disability. One should not expect chronic disability from an acute injury. Disability may remain in some instances but all too frequently the cause lies not in the injury itself but in its management, either by the doctor or by the patient. Many of the old concepts of athletic sequelae have to be drastically changed following more careful analysis. I do not think anybody is seriously concerned anymore about the athletic heart as a cause of decompensation in later life. Certainly the type of reasoning which holds that the ex-athlete tends to get fat because he quits the training he has been accustomed to is credulous to say the least. If he has an inherent tendency to get fat, he has at least postponed adiposity by training during his youth. Actually the majority of these people have enough pride in their physical prowess that they keep themselves in better physical condition because they have been athletes at some time in the past.

The knee joint is subject to some specific conditions which are prone to cause chronic changes. This joint is an extremely vulnerable one. It is subject to injury by the very nature of its anatomic structure, and particularly by its exposed position lying between two long bones with great leverage exerted on its ligaments. In a great many cases the original injury or original series of injuries is poorly managed so chronic changes occur. One of the most common of these is the degenerative change which results from intrinsic injury to the knee. A very common offender is the medial meniscus. The meniscus tears. There may or may not be episodes of locking. The activity of the patient is decreased to the point where he no longer competes in athletics. Yet, he continues to have a certain level of disability in the joint. The knee joint simply will not tolerate repeated episodes of catching, locking, or giving away, over a long period of time. The result is diffuse synovitis, over redundance of the fat pad, degenerative change in the patella, chondral marginal osteophytes and all the other components of chronic arthritis. Although we will grant that the best treatment would have been prevention, and although we still insist that the great majority of these abnormalities could have been obviated by initial good management, it does not help when we are faced with the patient who already has the problem.

There has been a great reluctance on the part of many orthopedists to undertake definitive treatment of the degenerated knee joint. One is prone to say, "This knee is so bad it will not respond well to operation," or "You are beyond the time when you need to be very active so you can get by with what you have." This procrastination simply magnifies the problem. If the patient, because of the knee, happens to lead a sedentary life, he may actu-

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ally die before the knee completely wears out. If the knee is less fortunate it may wear out first.

In my opinion the time to treat intrinsic conditions of the knee is when one first sees the patient. If one is fortunate enough to see the patient at age 16 immediately after the injury, this is wonderful. If one is so unfortunate as not to see the patient until age 45 and he already has marked degenerative changes, one should not withhold treatment simply because it will not give an ideal result. It should be recognized that one is not going to make his reputation on this particular case. A good result to this patient may be considerably less than the ideal. He may be very substantially improved in spite of the fact that he still has degenerative changes and he will accept this gratefully.

During examination of such a patient it is important to determine the extent of the pathologic changes present. In this article I will not attempt to go into the details of all the conditions to which the knee is subject. However, if the patient has chronic synovitis with effusion, there is usually some specific cause for it. It may indeed be primary in the synovium but this is unlikely. There is usually some underlying source of the irritation, and this should be diligently sought for and relieved. The chronic synovitis itself, of course, may be treated as one would treat any chronic arthritis. General measures such as enteric corticoids, salicylates and other of the multitude of remedies which are offered by our pharmaceutical friends may be used. Of even greater importance is local treatment providing this is local traumatic arthritis as the result of an injury many years before. To carry out local treatment with some degree of intelligence one must make an earnest effort to determine the exact disease. It is not sufficient to say he has chondral marginal spurs and to assume that this is the primary cause of the symptoms. It is much more likely that the chondral marginal spurs are the *result* of the condition, not the *cause*. On the other hand, they may be contributing to his disability and so may require local treatment. Thus it can be seen that it is necessary to evaluate this knee and determine if possible the following factors:

1. What was the actual initiating cause of the present disease?
2. Does this cause still exist?
3. Can it be remedied?

To illustrate this, let us say that a high school athlete had received an injury to his medial meniscus, that the medial meniscus still is present and still is locking on occasion. One could say with some confidence that he knows the cause of the original condition, that he knows the cause still exists and that this cause can be remedied.

Unfortunately, it is not always this simple. However, in this particular instance it would certainly be futile to treat the patient enterically, by local injection and the usual methods, meanwhile leaving a fragmented cartilage within the knee.

By the time the patient reaches you, the exact sequence of events may be quite obscure. One may be presented with a knee which shows malacic change under the patella, chondral marginal spurs around the joint lines, degenerative changes in the articular cartilages of the femur and tibia. There is also definite evidence of a lesion of the meniscus. Here the changes in the semilunar cartilages may be entirely degenerative and may indeed be the *result* of the original disturbance in the knee and not the *cause*. Analyzing this patient from the standpoint of treatment, one must try to evaluate the various conditions within the knee and decide in one's own mind just which of these conditions can be improved by treatment. In the example given above, certainly the offending semilunar cartilage should be removed. At the same time, however, one should not hesitate to remove osteophytes, to examine the patella critically for malacia and to resect the redundant inflamed fat pad. In short, the operation should treat all of the pathologic changes present and not simply the initiating cause of the trouble (Fig. 1).

The patella is extremely vulnerable and is very prone to degenerative changes so that so-called chondromalacia patellae is one of the most frequent conditions found in the chronically diseased knee. There are some instances in which the primary condition may indeed be in the patella. It is my conviction that these cases are infrequently spontaneous but are much more likely caused by some insult to the patella in the past. The fact that it is frequently bilateral may suggest that there is an intrinsic factor in the particular individual

which makes him susceptible. Indeed this may be true. Such anatomic variants as increased angle between the quadriceps tendon and patellar tendon, knock-knee, shallow patellar groove, may cause the patella to sublux laterally as it slides in the groove and so predispose to cartilage changes. However, one must not assume from the fact that it is bilateral that it cannot be traumatic since quite likely the same trauma is occurring to both knees.

I think that many of the cases of late degenerative change in the patella are actually due to direct trauma to the patella, many times even chondral fractures or fissures. In operating upon a knee for acute injury I have often seen actual fractures of the patellar cartilage though the x-ray examination was entirely negative. It is easy to visualize fissure type fractures resulting in gradual necrosis and prolonged chronic changes which may then be interpreted as degenerative arthritis when, as a matter of fact, it originated from an injury. Many knees fall into the chronic category in which the only lesion seems to be in the patella. There are many others in which the initial lesion seems to be in the patella and subsequent degenerative changes take place throughout the rest of the joint. There is in my opinion a still larger group where the initial lesion was a disturbance of joint rhythm. An example is the displaced semilunar cartilage with the malacia of the patella secondary to this because of the frequent sharp changes in direction of motion of the patella. The importance of recognizing these various causes lies in the fact that if the condition presently existing is to be treated intelligently, all of the factors should be considered. One would feel quite unhappy in removing a patella and leaving a chewed up meniscus.

If, following examination of the patient with chronic disease of the knee, one determines that there is serious chondral damage to the patella, a real problem is posed in management. Basically there are two modes of treatment: (1) elimination of the activity which causes the trouble, or (2) elimination of the trouble. The method to be chosen will depend to a large degree upon the inclination of the doctor and on the status of the patient. Thus, the 80 year old woman with patellar malacia and other changes in the knee could well be advised to stop going up and down stairs, eliminate squatting and reduce her activities to a level which the knee can well tolerate. This would be much preferable to operation since surgical treatment in this patient would probably present a serious problem in healing with degenerative tendons not responding well to repair. This same fact of poor general structure of the knee would make it necessary to carry out immobilization for a considerable period. This would in turn tend to promote stiffness and pain, the very things one is trying to prevent. Rehabilitation would be slow or impossible. Decision in such a patient would present no real problem.

At the other extreme is the active 35 year old man who likes his golf and whose livelihood depends upon regular activity of his knee including climbing, squatting, lifting (Fig. 2). He would be poorly advised to reduce his activities to the level at which he could "get by" since this not only would be a hazard to his livelihood and eliminate the pleasure of his leisure but he would face inevitable trouble later. With this amount of disease already present at 35 years of age and with serious degenerative changes, he would inevitably go on to such further changes that treatment would become imperative. Most would agree that such a patient should be treated surgically. The exact measures to be carried out of course would depend upon the lesion found. If the patella is found to be only slightly irregular with few changes, partial chondrectomy could be carried out. If the malacia is very advanced, with crab meat appearance of the cartilage and with exposed bone, patellectomy would be in order.

The larger group of cases will fall in the middle range where one will have to reach a proper decision as to the procedure which is best in that given case. It is axiomatic that "A normal patella is better than no patella but that no patella is better than an abnormal one." The exact point at which the patella should be sacrificed will vary considerably in the minds of different surgeons depending largely upon their experience.

The real problem in decision will come in the cases which are borderline. That is, the patient is neither very young nor very old. He does not intend to be an athlete, nevertheless, he does not like to have his activities restricted. His disease may be mild or may be severe. His occupation may be one demanding

excellent function of the knee such as a truck driver, or his occupation may be more sedentary such as an attorney. In such a case one must carefully balance his age, the desirable level of activity, the degree of disease in the patella, the condition of the remainder of the knee and come up with a decision as to what treatment is proper for this particular patient.

It must be emphasized again that chondromalacia patellae is probably not often a primary condition. The physician must avoid the pitfall of carefully deciding what to do with the patella and finding to his dismay that the patella is only part of the problem and that the decision he made in regard to the patella was ill suited to the disease found in the rest of the knee. The treatment of the patella itself may range from good advice to patellectomy. Specifically, nonoperative treatment consists of:

1. Protection against over-use.
2. Protection against acute or chronic trauma.
3. Local treatment of the inflammatory condition of the knee.
   - A. Aspiration of the effusion.
   - B. Injection with a corticoid.
   - C. Local heat.
   - D. Protection against motion during the acute episode.
4. Systemic treatment.

Systemic treatment is of considerable importance in polyarthritis which is a systemic disease. However, it is of much less value in the treatment of an isolated joint with chronic changes due to old trauma. The measures ordinarily used would be salicylates, cortisone derivatives, muscle relaxants, etc.

If nonsurgical treatment fails or if surgical treatment is elected primarily, the nature of the operation must depend entirely upon the type of lesion. One should be prepared to explore the knee very carefully. Careful x-ray study should be made to determine if possible the location of osteophytes or of chondral damage, loose fragments, or osteochondritic foreign bodies. Proper incision should be made to permit exploration of the knee, preferably a median parapatellar one, and attention should be paid particularly to the lesion previously suspected. That is, if one suspects an old degenerative medial meniscus, careful search should be made to determine its presence. If one believes preoperatively that there is damage to the posterior portion of the meniscus, he should be prepared to expose the posterior portion at operation and not overlook it simply because the anterior part of the cartilage seems to be intact. If there have been symptoms in the lateral compartment, it is not sufficient to make a medial parapatellar incision and treat the patella merely because disease found here could account for the symptoms. A second incision must be made to expose the lateral meniscus and thus avoid disappointment and the necessity for a second operation.

An effort should be made to preserve the patella and a partial chondrectomy should be done under the following circumstances: (1) a young individual with Grade 2 or 3 malacia so the degenerative portion of the cartilage can be removed and still leave some chondral covering; (2) the extremely elderly person with poor powers of rehabilitation but in whom diminution of activity will alleviate his symptoms; and (3) the middle-aged individual with Grade 1 or 2 malacia so that following chondrectomy a smooth undersurface remains.

On the other hand, patellectomy should be selected in: (1) the patient in the middle age group with rather advanced degenerative changes and in whom a relatively high degree of physical activity is desirable; (2) any case of Grade 4 malacia in which the inadequate patella would be a poor bearing; (3) cases of severe marginal spurring and degenerative ossified cartilage in which the undersurface of the patella is extremely hard and inelastic and pitted and ridged; and (4) in cases presenting a combination of severe involvement of the patella and of the apposing patellar groove of the femur (Fig. 3). For example, a patient may have only Grade 2 malacia of the patella and Grade 2 malacia of the femur. The combination would be inimical to good function whereas either alone might be quite amenable to less radical treatment.

In further discussion of the knee one should mention osteochondritis dissecans (Fig. 4). Purists will immediately say this does not actually represent an injury. However, I am prepared to dispute this statement since I believe a large majority of the cases of so-called osteochondritis dissecans actually are initiated

by trauma. One of the most common locations for osteochondritis dissecans is at the lateral margin of the articular cartilage of the medial femoral condyle just adjacent to the notch. This coincides with the attachment of the posterior cruciate ligament and I have seen repeated instances where the fragment was actually free except for the ligament attachment. I think many of these injuries are due to pull of the cruciate ligament. Many others, I am sure, are due to direct blows against the cartilage causing subchondral damage. There are many ways to treat osteochondritis in its initial stages and this should not be elaborated here other than to say that if the fragment actually is not displaced and if the patient is young it may be left alone. If the fragment is displaced it should be removed and the remaining bed curetted and the cartilage margins trimmed down to provide as smooth a surface as possible in order to encourage regeneration of the cartilage in the defect remaining. If the bed seems eburnated multiple small drill holes should be made with a fine Kirschner wire. Another method less popularly accepted has been to drill the fragment and tack it in with pegs or screws.

Whatever the method of early treatment, the thing we are concerned with now is the case which we first see as a late result. The cases will vary a great deal according to the original disease both as to the location of the lesion and as to its extent. An osteochondritic foreign body loose in the joint, a so-called joint mouse, is notorious as a cause of chronic synovitis with villus nodules, effusion, thickened synovium, in fact the typical picture of nonspecific synovitis. It has been pointed out that it would be futile to treat the synovitis and leave the fragment, and so the treatment must be surgical. The nature of the operation should depend upon the degree of disease. Many of these cases will have very extensive involvement with multiple foreign bodies, marked chondral marginal spurs and extreme synovitis ofttimes xanthomatous or villonodular in type (Fig. 5). True enough some of the symptoms may be relieved by the time-honored method of getting the patient off his feet but this is at best an inadequate method for definitive treatment. The main point of discussion must arise concerning the extent of the operation. Here, as has been pointed out previously, the decision as to the extent of the operation depends upon judgment as to what will give the best function. If a person is elderly and the main object of the operation is to prevent the knee from catching, causing a fall, one might be satisfied simply to remove the nodule with the least trauma possible. In a younger and more active individual this will not be satisfactory since the patient is not particularly pleased with merely elimination of the "catching" but continuing to have the symptoms of swelling, pain, disability.

Under such circumstances one should proceed to treat each condition as if it were an isolated one. The chondral marginal spurs should be removed if indicated and the area carefully smoothed out and sealed with bone wax. The patella should be carefully inspected and decision be made as to treatment just as one would in a primary patellar condition. Whether a synovectomy is done or not depends upon the circumstances. My satisfaction with synovectomy has not been great so I tend to avoid it if possible, particularly if I believe that by eliminating the remainder of the lesion I have removed the cause of the synovitis. Thus, I might be well satisfied by removing the foreign body, smoothing out the bed, taking off the chondral marginal spurs, even removing the patella and still leave most of the synovium undisturbed. If the fat pad is redundant it should be trimmed and hemastasis carefully secured, preferably by suture through the fat pad, plus electrocoagulation.

I do not believe one is justified in subjecting his patient to a life of inactivity simply because one cannot expect a normal knee joint following operation. Some of our most gratified patients are those who, after treatment, have a knee which is far from normal. It is so much better than it was before, that the treatment has been a godsend.

In examination of a knee one may occasionally find an osteochondritic foreign body which is asymptomatic, because it is attached to the synovium at some innocuous position. I see no justification in advising removal of such a body if it does not cause symptoms. The problem arises when the knee presents symptoms and such a foreign body is found. One must not assume that the foreign body is the cause of the symptoms simply because it is there, but one must convince oneself that

the symptoms are actually resulting from the foreign body in the joint. On the other hand, if one is going to operate upon the joint for some other reason or is going to do an exploratory arthrotomy, the foreign body should be removed at that time. I am sure we are all familiar with the patient who has been sent in for osteochondritis dissecans with a loose body, when it actually is the fabella, the sesamoid bone in the tendon in the lateral head of the gastrocnemius. Indeed it would be a futile search for a foreign body within the joint when, like the patella, it lies against the posterior condyle.

The most distressing sequelae of athletic injuries in the knee are the residual injuries of ligaments, the so-called unstable knee. This indeed presents a very serious problem. The major categories of injuries to the ligaments which cause late symptoms are injuries to the collateral ligaments and to the cruciate ligaments. The problem encountered is that of a middle-aged adult who is having increasing trouble in the knee (Fig. 6). He describes his knee as being "wobbly" and insecure, with gradually increasing disability. These cases are the result of sprains of the knee in which the healing has been incomplete. In the lateral ligaments it usually means the collateral ligament has healed but is too long. In the cruciate ligament it most frequently means it has been ruptured and has absorbed. One can have a surprisingly good degree of activity in the knee with a collateral or a cruciate ligament redundant so long as he maintains good muscle tone, good joint cartilage and normal menisci. He has long since learned the level of his activity, having given up hand ball, tennis and golf, indeed, all sports, and having learned to protect his knee in situations that are likely to cause trouble. As aging advances, however, the remaining ligaments become less elastic, the cartilage in the knee becomes less resilient, the menisci become sclerotic, chondral marginal osteophytes appear and he has the classical picture of chronic arthritis of the knee. This differs from the arthritis previously described in that there is the additional factor of instability. The basic lesion instead of being malacia of the patella or meniscus damage is in this instance instability. The problem magnifies itself by the fact that the very sequelae of instability cause increased relaxation. The joint cartilage becomes thin, the menisci narrow and flatten, the marginal osteophytes become larger and irritate the remaining ligament and so a vicious cycle is instituted.

Specific treatment here presents a very serious problem which is not materially lessened if the surgeon operates and does a "house cleaning" of the joint. This simply relieves the secondary symptoms of sclerotic menisci and exostoses and, indeed, may make the condition worse since it may add to the instability which is the cause of his trouble. It is difficult to recommend elimination of the basic problem. In some cases of a younger individual, one would be justified in shortening the collateral ligaments, particularly if it is the medial collateral one. I doubt if it is justifiable to reconstruct a cruciate ligament in such a case if one is considering an individual passed middle age. Reconstruction of a cruciate ligament gives the patient an uncertain prognosis. Often one finds himself faced with a collection of undesirable forms of treatment. It is undesirable to the surgeon to reconstruct the ligaments. The alternative of wearing a brace is not acceptable to the patient nor does he cheerfully accept your recommendation that he quit using his knee. In some instances this might mean he would starve or go on welfare. The final recourse to a fusion of the joint is bitterly resisted also. In younger active individuals with disabling instability, I believe one is justified in reconstructive operations particularly to the collateral ligaments. In the middle-aged group I have many times been gratified to obtain a satisfactory result following plication of the medial collateral ligament. Many other times I have been distressed with a poor result from this procedure. In the elderly I can see little justification for any extensive reconstructive procedures.

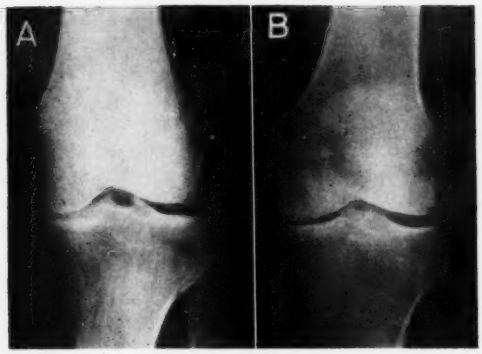
A word should be said about the patient who presents himself with primary synovitis of the knee. Typically there is no other intrinsic lesion. There should be no symptoms of damage to the meniscus, the patella should be relatively normal, the ligaments intact, the primary symptom being distressing and recurring effusion. This patient usually comes to the doctor because of swelling of the knee, otherwise being more or less asymptomatic. This condition may progress until the synovium is thickened, palpable and painful.

There may be recurring episodes of local heat and signs of inflammation. Here one must determine whether or not this is a sequela of chronic irritation of the synovium or an infectious type of arthritis. One should seek diligently for extrinsic causes. The general examination is very important, including temperature, pulse, general physical examination, and laboratory procedures as urinalysis, differential blood count, sedimentation rate. These should be negative in localized traumatic synovitis of the knee. Local treatment is important and should consist of aspiration of the effusion, a compression bandage, and some degree of immobilization depending upon the degree of symptoms, and the injection of corticoids and local heat. Many cases will respond to this type of therapy. A certain number of cases will not respond to any type of local treatment. Then one is faced with the question of whether an arthrotomy should be done or not. This is the type of case in which the primary synovectomy is done. Unless some specific cause can be eliminated by the operation, the result is likely to be unsatisfactory. If the knee has progressed to the point where there are other changes, they should each be managed as the situation demands. If the condition remains a true synovitis, as much of the synovium should be removed as possible, particularly the suprapatellar pouch and fat pad. I see no reason to remove the menisci if they are not abnormal. Most frequently a nonspecific synovitis is nonspecific only because we have failed to determine the cause.

One might conclude from the above that my suggestion for a remedy to chronic conditions of the knee is uniformly surgical. This is far from true. Many conditions of the knee will respond well to local nonsurgical measures. I have pointed out, however, that if there is definite disease which in itself tends to aggravate the degenerative changes in the knee, one is not justified in withholding operation simply because an ideal result may not be obtained. If one can no more than stop the progression of the degenerative change, operation may be justified. If this is necessary, the earlier it is done the less extensive it will need to be. To illustrate: If the ruptured medial meniscus is ultimately going to lead to degenerative changes in the knee with malacia of the patella, chondral marginal osteophytes, diffuse synovitis, and recurring effusion, such progressive change can be prevented by early primary removal of the meniscus. It is equally true that the meniscus should be removed whenever it is clear that it is the cause of the changes in the knee. If this diagnosis is not made until the patient is 45 years of age, or if the patient has refused operation until such a date, the best one can do is to operate at that time even though it is obvious that it should have been done long before. Surprisingly good results may be obtained if the degenerative change has not been too extensive. We have recently operated upon a physician who has been handicapped with a bad knee for over 20 years; he obtained a very excellent result because fortunately, he had few secondary changes in the knee in spite of the long duration of symptoms. He has now resumed his quail hunting with complete relief and, indeed, was operating within two weeks from the time of his own operation. Any rule that arthrotomy should not be done over the age of 50 would certainly have eliminated the gratification of this patient. On the other hand he could well have been spared his last 20 years of discomfort and gradually diminishing activity had he been willing to accept definitive treatment at the proper time. I believe we do a disservice to a patient when we advise him to live with his bad knee without giving him the benefit of a careful examination and a real decision as to the exact lesion present. To any particular patient "living with his knee" is a hard cross to bear. This is particularly true if he has been an athletic type individual. The casual locker room consultation with the comment "Well, you have got a trick knee, so baby it," or "This is a penalty you pay for having been a football hero" does him little service. Indeed, the vast majority of chronic degenerative changes in the knee as a result of past injury can be relieved to a very substantial extent by one method or another. The fact that we have suggested operation in many cases simply means there are many types of conditions which are amenable to such treatment. The majority of cases may respond quite well to nonsurgical measures if these measures are consistently and intelligently utilized.

The message I wish to leave is that the patient should be given the benefit of a careful history, an objective and comprehensive physical examination, a complete roentgeno-

FIG. 1



graphic survey and above all a real analysis of the degree of disability this condition is to this particular patient. One must consider his sex, his age, his occupation, his inclinations and his general physical condition. Only by such a realistic evaluation can one come up with the proper method of treatment for the individual case. Following such a regimen one will be extremely gratified at the degree of improvement which can be obtained in a knee which to the patient has become a well nigh insoluble problem.

Illustrative Material

Some illustrations (Figs. 1-6) and descriptions of cases follow.

FIG. 2

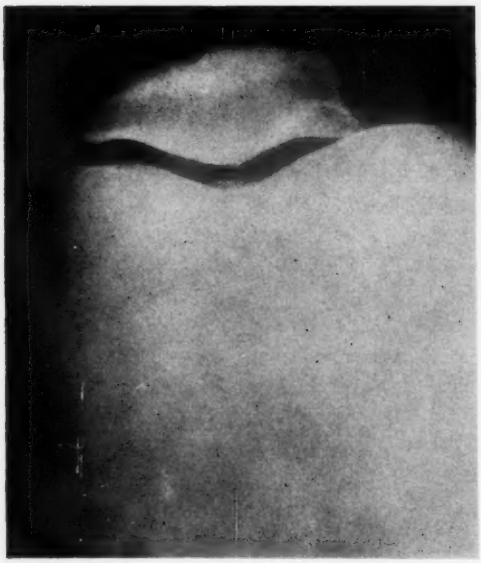


FIG. 3

Figure 1 illustrates two cases presenting the symptoms mentioned in the text, with long-standing chronic changes in the knee apparently initiated by injury to the meniscus.

In the case shown on the left, which is the older of the two, the patient was in his fifties. There are severe

FIG. 4

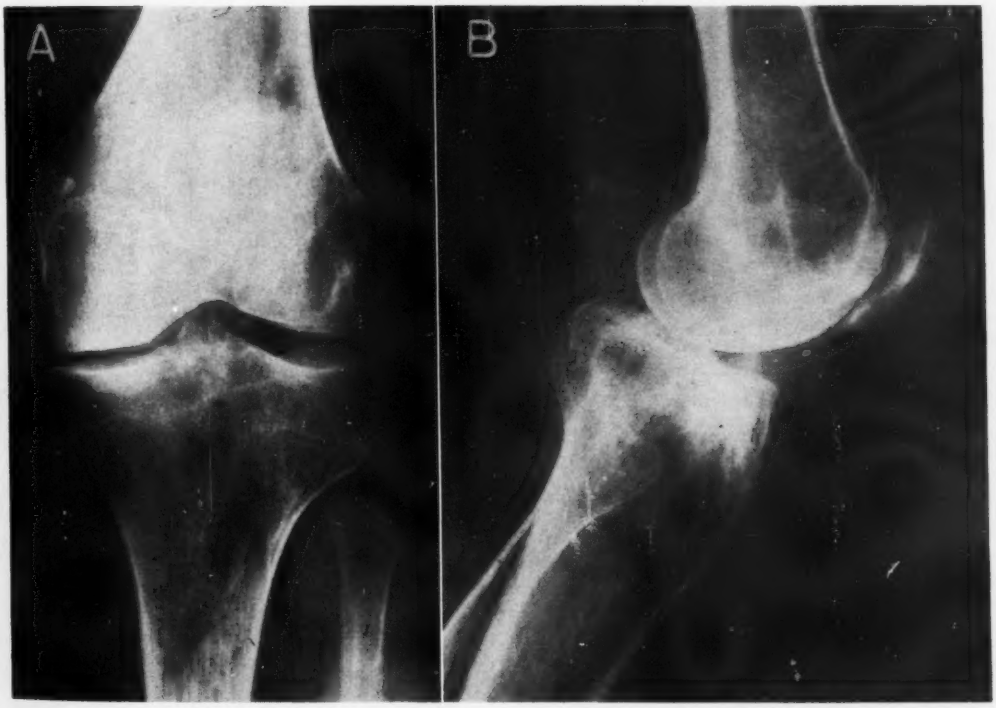
FIG. 5

degenerative changes—narrowed medial joint space, marginal osteophytes, calcification of the lateral meniscus and chondromalacia of the patella. This patient was treated by "general house cleaning" of the joint. The patella was removed, the marginal osteophytes and the extremely fragmented medial meniscus were removed as well as the calcified lateral one. Not only is he markedly improved but one has reason to believe that the progress of his degenerative change will be at least slowed by this procedure. He will admittedly have a very poorly functioning knee.

The example on the right hand shows a much earlier stage of the same change. This patient was 35 years of age, a very active person who was gradually slowed by increasing pain and disability in the left knee. In this instance the marginal osteophytes are less advanced. The patella did not have to be sacrificed, the medial meniscus was removed and an attempt was made to shift the weight-bearing to the lateral side of the joint by appropriate wedges on the shoes. He has been markedly improved following the operation and I have reason to believe he will not progress to the severe degenerative change shown in figure 1,A.

Figure 2 shows a silhouette view of the patella in a case in which the major lesion was confined to the anterior compartment of the knee. This patient had a history of injury to his patella many years before when hit by a baseball. At that time he had a fracture of the lateral margin of the patella. This bothered him for many years. At the time this film was made, he had palpable and audible subpatellar crepitation, painful

FIG. 6



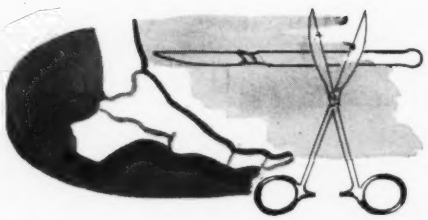
marginal osteophytes along the anterior portion of the femoral articular surface, particularly laterally, and increasing disability, with inability to squat, climb stairs, and particularly go downstairs. This condition was remedied by patellectomy and he now has a very useful knee with ability to climb stairs and to squat with minimal weakness in the leg. However, he has definite disability of this leg which probably could have been prevented by earlier operation. This case illustrates that operation should not be withheld at this stage simply because it is not as favorable as it would have been years before.

Figure 3 shows advanced post-traumatic arthritis of the knee, and serves to illustrate the point of contiguous involvement of the inferior surface of the patella and the patellar groove. This is not altogether typical because often there will not be the attendant changes in the remainder of the joint. It can be readily seen how the rough patellar groove would magnify the symptoms due to the patellar lesion.

Figure 4 is an instance of "osteochondritis dissecans" which I believe to be an osteochondral fracture. At operation this loose flap was found to be firmly adherent to about two thirds of the anterior attachment of the posterior cruciate ligament.

Figure 5 illustrates long-standing osteochondritis dissecans with amazingly large osteochondritic bodies in the joint. The superior one shows how these bodies become larger by steady accretion so what may originally have been a small cartilagenous body may become a very large fragment. This patient's condition had gradually deteriorated and was getting very much worse. Removing these bodies and trimming the osteophytes with partial synovectomy has resulted in considerable improvement although his knee is far from normal.

Illustrated in figure 6 is a classical instance of instability of the medial collateral ligament and anterior cruciate ligament with resulting degenerative changes in the joint incident to the extreme instability. This patient had injury to his knee many years before at which time presumably the anterior cruciate and medial collateral ligaments had been torn and had healed inadequately. At the time of my examination some 10 years following injury, increasing instability of the joint had developed to the point where even a brace did not effectively relieve his condition. At operation the fragmented medial meniscus was removed, the osteophytes trimmed away and reconstruction of the anterior cruciate ligament was carried out, as can be seen by the tunnels in the bone of the lateral condyle of the tibia and femur. This resulted in substantial reduction of the instability, although he still had a considerable increase over the opposite knee. He has been able to discard his brace and, although his knee certainly is not capable of athletic endeavor, he is sufficiently improved that he is able to go without external support.



Practical Management of Snake Bite in Louisiana

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L. P. LAVILLE, JR., M.D.,† *Baton Rouge, La.*

Morbidity and mortality are directly related to the amount of venom injected at the time of the bite. The authors suggest the use of standard methods of treatment of snake bite.

SOME 2,000 TO 3,000 POISONOUS SNAKE BITES occur annually in the United States, with a fatality of 10 to 35 per cent.[1] Because of this relatively small number of bites, few physicians have had extensive experience in the management of these accidents. In a four and one-half year period (July 1955 to January 1960) 55 victims of ophidian venenation were treated without a mortality at the Lallie Kemp Charity Hospital, a rural state hospital in southeast Louisiana. The snakes inflicting the bites were 14 copperheads, 13 rattlesnakes (ground or pygmy rattler), 11 moccasins and 17 unidentified. The unidentified were classified as probably venomous on the basis of the fang marks at the site of the bite. Seventy per cent of the bites occurred on the lower extremities and 30% on the upper extremities. The occurrence was most frequent in the early morning or late afternoon. The greatest incidence of bites was in early spring and summer, the periods when snakes are out of hibernation and most active. Thirty-seven of the patients in this study were under 16 years of age. There were 36 males and 19 females. Thirty-two of the patients were white and 23 were colored. The average lapse of time between the bite and hospitalization was one to two hours.

Treatment

Treatment consisted primarily of administration of antivenin, incisions and suction, lymphatic tourniquet, antibiotics and appropriate antitetanus treatment. The average hospital stay for all patients in this study was 3.7 days. Twenty-one of the patients received cortisone in addition to the therapy mentioned. The average hospital stay for these patients was 4 days. Nine other patients were similarly treated with the exception that incisions and suction were not employed, the average hospital stay being 2.8 days. No selection was made of these groups.

Three serious complications occurred. The first involved a 6 year old white boy who was bitten on his left index finger by a water moccasin. He was treated with antivenin, lymphatic tourniquet and incisions with suction. Severe edema and inflammation about the wound were soon followed by necrosis. Tissue damage progressed and after one month the proximal interphalangeal joint was exposed and on x-ray examination osteomyelitis was evident. Despite all therapeutic attempts, the wound failed to respond and an amputation at the metacarpal phalangeal joint was necessary (Figs. 1,A-C).

The second case occurred in a 9 year old white child who was bitten on the right index finger by a water moccasin. Edema and erythema were marked in the area of the bite. Treatment consisted of antivenin, incisions with suction and tourniquet. On the sixth hospital day, the patient was discharged with resolution in the soft tissue swelling, but with decided pain in the proximal interphalangeal joint. Subsequently, extension of this joint was limited to 160° and there was x-ray evidence of epiphysitis. Despite physiotherapy there was no improvement in function and pain persisted. Surgical ankylosis was performed with good results (Fig. 2).

The third complication was seen in a 5 year old colored boy who was bitten on the right calf by an unidentified poisonous snake. He was seen 7 hours after the bite with two fang marks and associated edema and erythema adjacent to the bite. The "standard therapy,"

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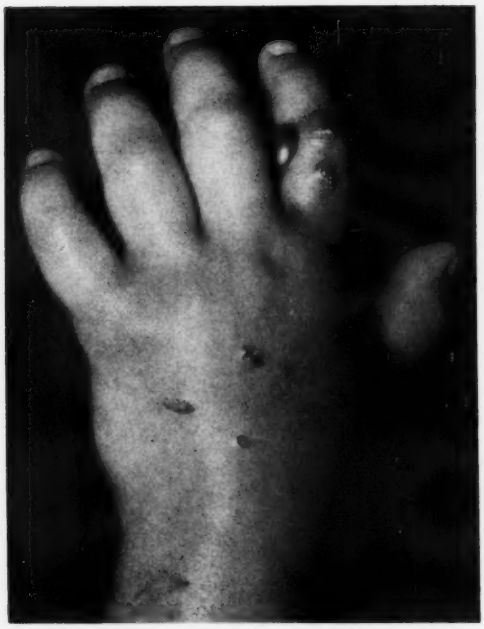
FIG. 1, A



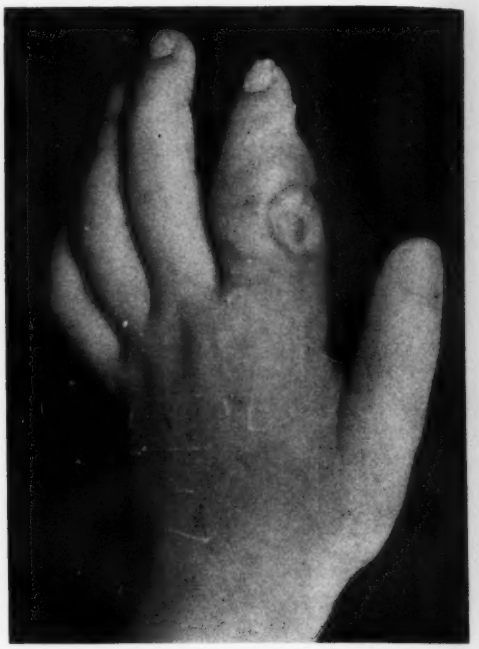
A 6 year old boy bitten on his left index finger by a water moccasin developed infection and necrosis and had to have finger amputated. (A) Hand 3 days after bite on June 18.

including antibiotics, was used. On the third hospital day there was a temperature elevation to 103° F. Chest x-ray film revealed a slight increase in the perihilar bronchovascular markings (Fig. 3,A). The child remained febrile. X-rays 3 days later demonstrated an extension of the pulmonary findings to include bilateral fluffy infiltrates of pneumonitis (Fig. 3,B). X-rays on the seventh hospital day revealed

FIG. 1, B

(B) X-ray film on July 16 showing osteomyelitis, septic arthritis, dislocation.

FIG. 1, C



(C) Appearance of hand on July 22 with the joint exposed.

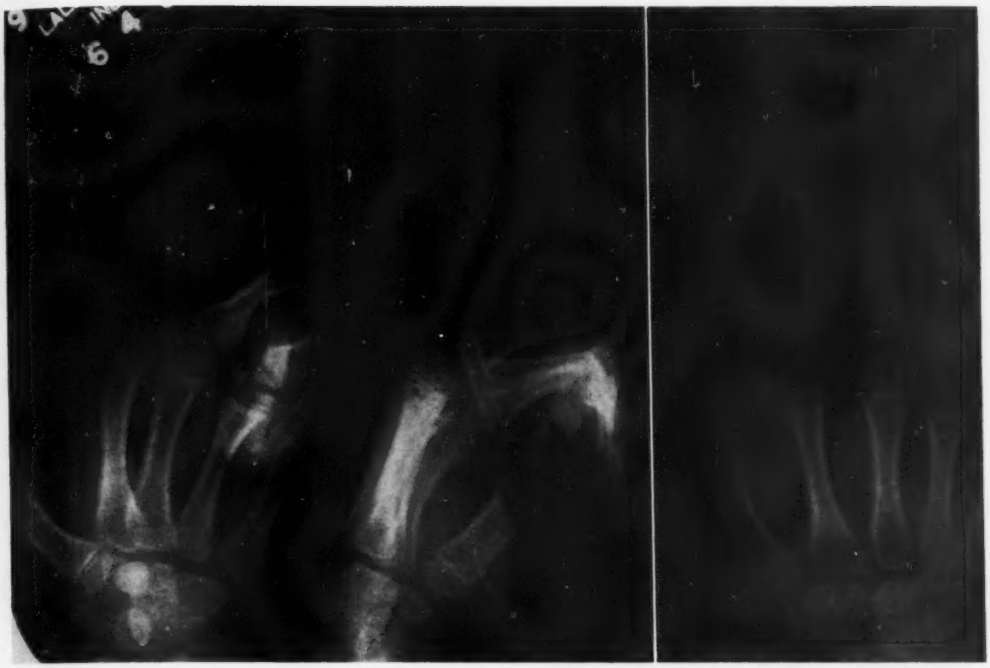
definite clearing and the patient's clinical course improved markedly (Fig. 3,C).

The interesting facet of this case is that the child's hematocrit steadily fell from an initial value of 42 to 26 by the seventh day. It was inferred that hemoglobin breakdown products present in the lungs, resulting from hemolysis of red blood cells by the snake toxin, caused the x-ray findings. This was the only patient with evidence of hemolysis. No hematuria was found in the cases tested. This is in keeping with Swartzwelder's 306 cases in which there was only one episode of transient hematuria.[2]

The most important point in the diagnosis of poisonous snake bite is identifying the bite as being venomous. This is readily done if the snake is killed and positively identified. Identification of the pit viper can also be made by the characteristics of the bite.[3] The fangs of a poisonous snake produce two distinct punctures. A row of minute wounds from the small teeth of the lower jaw may or may not be present (Fig. 4). Edema, erythema and pain are soon associated with the venomous wound.

The venoms injected by pit vipers are com-

FIG. 2



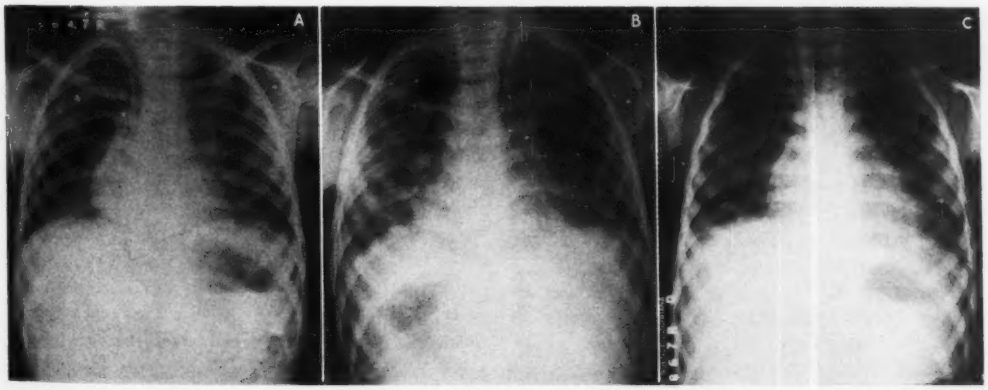
Nine year old boy bitten on right index finger by a moccasin developed a painful joint and required surgical ankylosis.

posed chiefly of proteins and enzymes.[4] These toxins are hemolysins, hemocoagulins, proteolysins and cytolysins. Death due to pit viper toxin has been shown to be primarily the result of hemorrhage or obstruction in a vessel supplying a vital organ, most often the brain.

After the diagnosis of ophiotoxemia, or when poisonous snake bite is established, treatment should begin immediately. The two primary objectives in the treatment of a bite by a pit viper are:

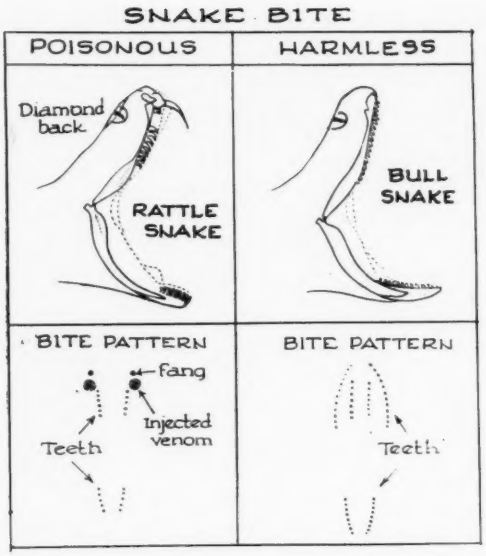
1. To prevent the absorption of the venom.

FIG. 3



Chest films of a 5 year old boy who developed a pneumonitis secondary to hemolysis of red blood cells on the third post-bite day. (A) Third post-bite day, September 23, increased perihilar bronchovascular markings. (B) Sixth post-bite day, September 26, bilateral pneumonitis. (C) Ninth post-bite day, September 29, shows clearing of chest.

FIG. 4



This shows characteristic wounds from a poisonous rattlesnake and a harmless bull snake.

2. To neutralize the venom already absorbed so that a lethal dose will not be in the circulation at any time.

The most important means of combating toxin is by the administration of antivenin.[5] Antivenin (Nearctic Crotalidae Polyvalent) is effective in the treatment of the pit viper bites of this country, namely moccasins, rattlesnakes and copperheads.[5] This horse serum antitoxin remains stable at room temperature for at least 5 years. Gingrich and Hohenadel[6] have shown that 10 cc. of antisera are able to neutralize 15 to 20 mg. of any North American pit viper venom.[6] Twenty-five milligrams of toxin is considered the minimal lethal dose for the average size man.

The average diamond-back rattlesnake injects 200 mg. of venom at a bite or about 9 lethal doses; the average cottonmouth moccasin injects 150 mg. or 6 lethal doses; and the copperhead 45 mg. or nearly 2 lethal doses.[7] The average adult can neutralize about 25 mg. of toxin. It has been shown that 4 to 5 lethal doses or 100 mg. of toxin can be removed by incisions and suction, leaving 100 mg. of toxin to be neutralized. Therefore, for minimal safety 4 to 5 ampules of antivenin are required.[7] Accurate identification of the snake which inflicted the bite is a guide to the amount of antivenin to administer. The clinical response also indicates the amount of antisera to give. After the initial dose is injected, additional antivenin is administered according to the progress of edema, erythema or systemic manifestations. If the bite involves a superficial vein or the patient demonstrates severe systemic reactions, doses of antivenin may be rapidly administered intravenously. Larger doses of antivenin are necessary in treating snake bites in children. After appropriate testing for sensitivity to horse serum, the antivenin can be administered intravenously or intramuscularly.

The second most efficient means of combating ophiotoxemia is by incisions and suction. Using local anesthesia, incisions are made into the subcutaneous tissue at the site of the fang marks. Additional incisions are made as demanded by the severity of the bite. Suction is applied by whatever means available. An electric suction apparatus can be used effectively by placing an ear speculum, inserted into the tubing, over the wound. Interrupted suction is applied.

The efficiency of suction was well demonstrated by Dr. Dudley Jackson.[7] Dogs bitten by venomous snakes were treated by incisions with suction and the serum obtained by suction was injected into normal dogs. The bitten dogs treated by incisions and suction lived. The dogs injected with the sera obtained from the bitten dogs died.

The absorption of pit viper venom from subcutaneous tissue is relatively slow.[8] For this reason, many authorities are skeptical of the benefits gained from the use of a tourniquet.[8] This is especially apparent when antivenin is administered shortly after the bite and the venom thereby soon neutralized. If employed, the tourniquet should only be tight enough to restrict lymphatic return. Disastrous results have been reported from the over-zealous employment of a tourniquet. Dependency of the affected part may also be used to retard the absorption of toxin.[8]

The ligation-cryotherapy (tourniquet and cold) method of treating snake bite has been advanced by Stahnke.[9] He pointed out that with cold there is retarded chemical and bacterial action. With ligation there is slower release of venom. Critics of this method recognize the "L-C" treatment as only an adjunct at best.[10]

When antivenin was first prepared by in-

jecting the snake toxins into horses, several animals died as a result of infection at the injection site.[11] This problem was solved when bacterial contaminants in the toxin were destroyed before the toxins were injected. Several investigators reported deaths in experimental animals which resulted in part from severe infections at the site of toxin innoculation.[12] In Swartzwelder's series of 306 cases, one of the three fatalities was from septicemia.[2] Prophylactic antibiotic therapy is a definite aid in the management of snake bite.

Cortisone, other than to combat anaphylaxis which might result from the administration of horse serum, has been shown by several authors to have no beneficial effect in combating ophidian venenation.[10] Similarly, antihistamines seem to have no direct beneficial effect.

Adjunct therapy toward allaying restlessness and apprehension should be employed. The snake bite victim should be kept quiet and moderately sedated. In severe cases, intravenous fluids and blood transfusions should be administered to combat shock. Appropriate antitetanus therapy should be employed in all victims of pit viper bites.

Discussion

The therapy of pit viper bites is directed toward neutralizing the toxin injected or preventing its absorption. The effectiveness of treatment is similarly dependent on the amount of toxin injected. Each snake bite victim is an individual problem. In Swartzwelder's series from Charity Hospital of New Orleans there were three mortalities.[2] Lallie Kemp Charity Hospital is 80 miles from New Orleans Charity Hospital and, although the snake bites in these two series are comparable, no fatalities occurred at Lallie Kemp Charity Hospital. In sharp contrast to these reports, Jutzy and associates[13] reported a series of pit viper bites from the Panama Canal Zone in which there was a mortality rate of 30.4 per cent. In the southwestern United States where large rattlesnakes are prevalent, the mortality ranges between 3 to 10 per cent. The discrepancy in mortality is thus thought to be due to the amount of crotoxin that the individual pit vipers are able to inject. Large rattlesnakes are capable of injecting nearly 5 times the amount of toxin as the copperhead.[5] Similarly the *fer de lance,* which accounted for most of the fatalities in the Panama series, is capable of injecting a large quantity of crotoxin.[13] Victims of bites of the more virulent pit vipers should therefore be treated by all means described to neutralize the toxin and prevent its absorption. On the other hand, victims of less virulent copperheads and ground rattlesnakes need to be treated with the same watchful expectancy but with more conservative therapy.

In this series 9 victims of pit viper bite were treated with antivenin but without incisions and suction. There was no mortality. Further, the average hospital stay for these patients was 2.8 days whereas the over-all average was 3.7 days. The administration of adequate antivenin plus the fact that these pit viper bites were less toxic seem to have been the deciding factors in the lowered morbidity.

If incisions and suction can be safely postponed in the less virulent bites, a definite advantage is gained. Two complications in this series were severe skin necroses. This soft tissue necrosis was primarily due to the snake toxin, yet may have been enhanced by the multiple incisions. Further, it is believed that open wounds provide a second nidus for infection. The necessity for active, early, aggressive therapy employing all approved methods cannot be too strongly emphasized when a large snake with virulent venom is involved.

Schottler[14] showed that cortisone did not significantly alter the course of victims of pit viper bites and our study supports his view. Those patients who received cortisone therapy, in addition to the standard therapy, remained in the hospital an average of 4 days as compared with the 3.7 days for the over-all series. There was no significant amelioration of symptoms attributable to cortisone.

Bacterial contaminants are always associated with poisonous snake bites and the necrotizing nature of the venom greatly increases infection; therefore, the prophylactic use of antibiotics is strongly recommended.

Conclusions

Fifty-five cases of pit viper poisoning treated at a rural general hospital in southeastern Louisiana without a fatality are presented and the therapy is discussed.

References

1. Porges, N.: Snake Venoms, Their Biochemistry and Mode of Action, Science 117:47, 1953.
2. Swartzwelder, J. S.: Snake Bite Accidents in Louisiana with Data on 306 Cases, Am. J. Trop. Med. 30:575, 1950.

3. Pope, C. H., and Perkins, R. M.: Differences in the Patterns of Bites of Venomous and of Harmless Snakes, Arch. Surg. 49:331, 1944.
4. do Amaral, A.: A Textbook of Medicine. Philadelphia, W. B. Saunders Company, 1951.
5. Crimmins, M. L.: Poisonous Snakes and the Antivenin Treatment, South. M. J. 22:603, 1929.
6. Gingrich, W. C., and Hohenadel, J. C.: Standardization of Polyvalent Antivenin. Venoms, Am. Ass. for the Advancement of Science, p. 381, Washington, D. C., 1956.
7. Jackson, D.: Treatment of Snake Bite, South. M. J. 22:605, 1929.
8. Leopold, R. S., Huber, G. S., and Kathan, R. H.: An Evaluation of the Mechanical Treatment of Snake Bite, Mil. Med. 120:414, 1957.
9. Stahnke, H. L.: The L-C Treatment (Ligature and Cryotherapy) of Venomous Bites or Stings, Am. J. Trop. Med. 2:142, 1953.
10. Wood, J. T.: A Critique on the "L-C" (Ligation and Cryotherapy) Treatment of Snake Bites, South. M. J. 49:749, 1956.
11. Pope, C. H., and Peterson, L. W.: Treatment of Poisoning with Rattlesnake Venom; Experiments with Negative Pressure, Tourniquet and Bulb Suction, Arch. Surg. 53:564, 1946.
12. Allen, F. M.: Mechanical Treatment of Venomous Bites and Wounds, South. M. J. 31:1248, 1938.
13. Jutzy, D. A., Biber, S. H., Elton, N. W., and Lowry, E. C.: A Clinical and Pathological Analysis of Snake Bites in the Panama Canal Zone, Am. J. Trop. Med. 2:129, 1953.
14. Schottler, W. H. A.: Antihistamine (Phenergan), ACTH (Adrenocorticotropin Hormone), Cortisone and Hydrocortisone (Adrenocortical Preparations) and Anesthetics in Snake Bite. Am. J. Trop. Med. 3:1083, 1954.

(The authors will supply more reference titles if the readers so request these.)

Make Plans to Attend—
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Evaluating the Suicidal Risk*

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No matter what his type of practice, the doctor sooner or later, and at intervals will have under his care a patient who has attempted or threatened suicide. Under no circumstances can he dismiss these symptoms as insignificant. His is the responsibility of evaluating the patient's personality and motivations, for many are the successful suicides shortly after an abortive attempt.

"I have a hundred times wished that one could resign life as an officer resigns a commission," wrote Robert Burns in a letter of 1788.

EVERY PHYSICIAN during his career is confronted with the patient who no longer wishes to live. Life has lost its meaning and purpose, so suicide is viewed as a panacea for the patient's problems. The recognition, evaluation, management, and prevention of these cases is a responsibility which the physician cannot evade, whether psychiatrist or nonpsychiatrist. Medical responsibility is well illustrated by Motto who investigated 175 consecutive suicides and 197 unsuccessful suicide attempts. He found that at least 40% of the suicides and 60% of the attempted suicides were, or had been under medical care within the preceding 6 months. In 14 cases the attempt at suicide occurred on the same day the person saw the physician. One third of the suicidal attempts were by the use of barbiturates medically prescribed.

Motto[1] further reported that psychiatrists evaluated only 11% of successful suicides and 7% of attempted suicides. He noted that the burden of evaluation falls mainly on the shoulders of the general practitioner and internist.

A recent report showed that there are approximately 17,000 successful suicides annually, in addition to at least 100,000 suicidal attempts.[2] These are only approximate figures as many patients and their families attempt to conceal the episodes due to embarrassment, fear of losing insurance benefits, etc. The purpose of this paper is to present practical hints in the evaluation and management of the suicidal risk.

*Read before the Section on Neurology and Psychiatry, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

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Personality Types Prone to Suicide

A variety of personality structures are prone to suicide. No single diagnostic category is helpful in predicting suicide potential. Zilboorg[3] concluded, "Evidently there is no single clinical entity recognized in psychiatry immune to the suicidal drive. It is to be viewed as a reaction of a developmental nature which is universal and common to the mentally ill of all types and probably also to many so-called normal persons." A prominent feature associated with many potential suicides is depression. This may vary from the intense, severe psychotic depression, whether due to so-called involutional melancholia (involutional psychotic reaction), manic-depressive psychosis, to the less severe psychoneurotic depression. The difference is mainly quantitative. Thus, evaluating the depth and severity of the depressive symptoms is the major diagnostic task, regardless of the diagnosis of paranoid schizophrenia, alcoholism or psychoneurosis. The character and behavior personality disorder also constitutes a large number of suicidal attempts. The latter personality is characterized by impulsiveness, poor judgment, "acting-out" behavior, and need for immediate gratification. This individual usually tries suicide as a gesture in an attempt to manipulate and control the environment to yield desired objectives.

Signs and Symptoms of Depression

How is depression then to be recognized? One of the prominent initial features is a generalized loss of interest, energy and drive. The cardinal symptoms of anorexia, insomnia, weight loss, sadness, guilt feelings and self-depreciation are easily recognized and need no repetition. What needs emphasizing is the role of depression in hypochondriacal states and the importance of so-called "depressive equivalents." In many instances isolated or recurrent

bouts of depression never requiring hospitalization have occurred. These illnesses will frequently be missed unless a careful history is taken. Headaches, back pain, abdominal symptoms with no organic etiology, and over-concern about minor physical symptoms are prominent in depressed patients.

Indicators of Potential Suicide

Psychiatric evaluation of the suicidal risk involves a high index of suspicion. Although there is no clear-cut infallible means of evaluating the suicidal risk, a methodical investigation is of great value. The basis of the evaluation lies in the psychiatric history and interview, as well as recognizing the signs and symptoms of depression. The following outline which I employ may serve as a guide:

(1) Ask about whether suicidal intent has been communicated to others. One of the most significant questions to ask is whether the patient has mentioned suicidal intent to his physician, family, friends, minister, etc. A recent study by Robins and associates[4] revealed the striking finding that 69% of 134 consecutive successful suicides had communicated suicidal ideas and that 41% had specifically stated that they intended to commit suicide. Furthermore, these investigators found that in the majority of instances the suicidal communications were of recent onset (months), repeatedly verbalized and expressed to many persons. Chronic alcoholics had a somewhat greater tendency than other patients to specifically state suicidal intent.

(2) Explore the circumstances surrounding the suicidal attempt. Was the patient drinking, out of a job, financially embarrassed, separated from his spouse, or "unlucky in love"? Did he leave a "note," and if so, to whom was it addressed? The latter is frequently of value in understanding the psychodynamics of the attempt. Was the patient socially isolated and lonely with little prospect of increasing his human contacts? Did he have a feeling of uselessness and helplessness in ever ameliorating his situation?

(3) Inquire about the history of previous episodes of depression and mental illness. A striking finding by Robins, Schmidt and O'Neal[5] and Batchelor[6] in their studies of patients 60 and over revealed that over 90% of their patients had clinically diagnosable mental illness. Ninety per cent of Batchelor's 47 cases and 84% of Robins' 19 cases were accounted for by three categories: depression, chronic alcoholism, and chronic brain syndrome. Robins, furthermore, stated that in his series of 134 consecutive cases of suicide, 75% were suffering from two illnesses — manic-depressive disease, depressed phase (50%) and chronic alcoholism (25%).

(4) Inquire about previous suicidal attempts. A history of several or more suicidal attempts is a disturbing sign even when occurring in those with character and behavior disorders. This is true since occasionally these patients may commit suicide accidentally. It cannot be overemphasized that these patients who are disturbed sufficiently to resort to suicidal gestures are also emotionally ill and in need of psychiatric treatment. Their gestures should always be taken seriously. Physical signs, such as transverse scars on the wrist or neck, may suggest previous suicidal attempts.

(5) It is not enough merely to have the patient admit suicidal attempts. It is important to learn his attitude toward these attempts, whether it has changed and, if so, in what way. Is he sorry that he did not succeed, or grateful that the attempt was thwarted. Frequently the patient minimizes the attempt and tries to evade any efforts at treatment. Careful attention to the patient's speech and facial expression is of special value. Evaluation immediately after the attempt, when the patient's sensorium is clear, frequently provides the most reliable information. Waiting several days after the attempt often allows the patient to rebuild his ego defenses and deny suicidal intent. Thus, the physician may readily be deceived. Evasiveness, indecisiveness and hesitancy should cast much suspicion in the examiner's mind. Likewise, the statement, "I don't know why I did it. I don't think I wanted to kill myself," is hardly reassuring as a preventive to future attempts.

(6) Ask how the proposed suicide would be committed. Definite ideas such as the purchase of a weapon or drugs is an ominous sign. Oliven[7] states that the means employed in the suicidal attempt may be an indication as to its seriousness. Most suicidal gestures with less serious intent may be characterized by such evidence as superficial lacerations of the wrists and palms, sublethal doses of aspirin, tranquilizers, sedatives, and turning on the gas stove with doors and windows opened, etc.

Psychotic patients usually employ more serious and sometimes multiple means of attempting suicide. One schizophrenic woman inflicted multiple deep lacerations of both wrists and chest, suffered third degree scalp burns from putting her head in a furnace, and inflicted on herself a depressed skull fracture with a hammer all within the span of 15 minutes.

(7) Awareness of the role of age and sex is especially important. Sainsbury[8] has noted that in both sexes suicide increases with age, especially after 60 in men. Schmidt[9] classified 120 suicidal attempts as serious or not serious. He noted that the average age in the serious group was 48 and in the "not serious" 34. Capstick[10] recently concluded that 48% of 351 persons who committed suicide over 60 were depressed.

Even though we are aware of the importance of mental illness and depression as precursors to suicide, especially in patients over 60, further investigation into interpersonal and dynamic factors is very much needed. We do not yet know what predisposes a small percentage of these seriously depressed patients to commit suicide.

Questioning the Suicidal Patient

Oliven[7] declares that the danger of putting ideas in the patient's mind is negligible and that there is "no bonafide case of mobilization of suicidal impulses caused by questioning." An abrupt question such as, "Do you want to kill yourself?" may be so startling that the patient is often forced to vigorously deny suicidal intent. The author has found the following graduated series of questions quite acceptable to most patients:

How are your spirits today? Do you feel depressed or blue?

What do you feel like doing when you feel this way (blue, depressed)?

Have you thought of going to sleep and not waking up? (Frequently the patient can admit this, where he would otherwise deny suicidal intent.)

Have you thought of doing away with yourself?

Are you thinking of suicide now? Recently?

Is anybody (voices) telling you to do away with yourself? Broached in this manner, the patient's defenses are less formidable and he is capable of discussing his underlying thoughts and feelings.

Answers to these questions vary widely. If the patient says "No," but refuses to elaborate, the physician can hardly be reassured. On the other hand, a qualified denial is encouraging by such statements as, "I've thought of suicide but I can't do it. I've got my wife and family to think of. Besides, it's against my religion."

Following a suicidal attempt it is of great importance to add several other questions as follows: "Do you feel you need psychiatric help?" The patient who can acknowledge emotional illness and requests psychiatric treatment is certainly a far better risk than the patient who denies it. Additionally, it is useful to ask, "Do you think this will happen again? If not, why not? What would you do differently to prevent this from happening again?" Frequently the patient will feebly say, "I don't know, Doctor," which can hardly be considered supportive. On the other hand, a qualified elaborated statement such as, "I'm going to get help," or, "I'm going to join AA," etc., is of considerable relief. Asking, "What would have prevented this (suicide attempt) from occurring?" frequently provides useful clues to the psychodynamics of the case. If the patient has had suicidal preoccupations in the past but steadfastly denies them currently, it is important to learn whether there have been significant changes in his attitude or life situation which may provide reasonable safeguards against any future attempts or gestures at self-destruction.

Example

I have recently evaluated 35 suicidal attempts and gestures in military personnel and civilian dependents at a large military training base. An example from this series, illustrating the above method of evaluating the suicidal risk, will be described:

A 28 year old Staff Sergeant and veteran of 10 years of military service was admitted to the base hospital in a semicomatose state following the ingestion of an unknown number of Doriden (glutethimide) tablets. He stated that during the preceding 4 years, following a divorce, he had a "feeling of being lost and not belonging." A second marriage lasted less than 2 years. Thereafter, except for a few military acquaintances, the patient saw himself as increasingly alone in the world. During the month prior to his attempted suicide, he experienced insomnia, restlessness, and suicidal ruminations. A precipitating factor involved an unfortunate conversation with a maternal-like acquaintance who suggested that the patient stop his monthly allotment check to his first wife, who had not seen the patient in over two years. She implied that his first wife might be secretly married but con-

tinuing to "use" him as a "meal ticket." He had no desire to "check" on her statement, and felt hopeless and impotent. Several hours later he drank heavily at several local bars, returned to his barracks and took the sleeping pills.

A review of his past history reveals marked early emotional deprivation. The patient is the youngest of 6 children. His father, an alcoholic, died when he was 5 months old. During his early developmental years his mother, a cold, aloof woman, held a variety of menial jobs to keep the family going but clearly could not respond to the patient's dependency needs. He recalled, "My family was never affectionate." A brother, 14 years older, was described as "mean and sadistic." The patient graduated from high school with average grades and thereafter entered military service, achieving a good record.

Examination of the mental status revealed a deeply preoccupied young man with a sad, depressed facial expression. He thought he had made a "mess of my life" and "felt hopeless and useless." Strong self-depreciatory and self-condemnatory statements were voiced. He stated that he had intended to commit suicide and was not happy that he was "rescued." The Sergeant spoke in a low-pitched, almost inaudible voice, stating, "I've never been afraid of death."

Assessment of suicide potential revealed that he had not communicated suicidal intent. He was rushed to the hospital by ambulance after being asleep for a number of hours and failing to respond when aroused. Previous episodes of depression and suicidal ruminations were admitted but he "was always able to pull out of them on my own." He had been seen by a psychiatrist several years earlier for a few visits, but did not continue. He denied previous personal or familial suicidal attempts. Although suicidal ruminations had been present for at least one month, the final decision occurred impulsively. A clinical diagnosis was made of neurotic depressive reaction, severe, in a passive-dependent personality. His suicidal attempt was considered serious.

Because of the patient's subsequent strong motivation for psychotherapy, he was given an immediate appointment following hospital discharge and followed closely for the next several weeks while simultaneously receiving an anti-depressant drug. His prior good service record and strong motivation for psychotherapy encouraged the therapist to recommend retention in the service. Currently, he is being seen weekly, and at a 4 month follow-up shows considerable improvement in mood, assertiveness, and level of performance.

Management of the Suicidal Attempt

All too frequently in treating the suicidal attempt, the patient receives only supportive medical care. His stomach may be lavaged, his tendons sutured, and his brain stimulated with narcoleptics. He is then dismissed without psychiatric evaluation or consultation only to attempt suicide again in many instances.

There is general agreement among psychiatrists that the seriously suicidal patient is best managed in a psychiatric hospital. Good working relationships between the referring physician and the patient's family cannot be overemphasized. Relatives should be instructed about the danger period immediately following hospitalization so their watchful observation will not be relaxed. Frequently the patient may again attempt suicide just as he appears to be convalescing successfully. Shneidman and Farberow[11] noted that half of their 32 patients committed suicide within 90 days after discharge from the hospital. Should the patient again voice suicidal threats to the family the latter should be instructed to contact the family physician immediately. Miller, Fellner and Greenfield[12] emphasize the importance of giving the patient a return appointment after each office visit and recommend that he return weekly for refills of medicine. Such a practice diminishes the possibility that physician-prescribed barbiturates and tranquilizers can be used in a suicidal attempt.

Although the immediate concern in managing the suicidal patient is to prevent a suicidal attempt, treatment must extend beyond this level. Depression, like alcoholism, is only a symptom of underlying emotional illness. Its causes need to be adequately understood so psychotherapy can effectively enable the patient to resolve his underlying conflicts. Antidepressant medications such as imipramine HCl (Tofranil), iproniazid (Marsilid), and a host of similar drugs, as well as electroconvulsive therapy frequently produce only a temporary remission of symptoms. They do not cure and do not alter the patient's basic personality structure.

Summary

The key to successful management of the suicidal patient lies in early diagnostic evaluation and early treatment. A cardinal feature in early diagnosis is the recognition of the degree and depth of depression in its various manifestations. An outline for evaluating the suicidal risk patient is presented with special emphasis on the communication of suicidal intent. A series of questions is described to help evaluate the seriousness of suicidal intent as distinguished from the histrionic suicidal gesture. An illustrative example is presented. Finally, the management and prevention of suicide are discussed with special emphasis on securing adequate family cooperation and developing sound working relationships between the general physician and the psychiatrist.

References

1. Motto, J. A., and Greene, G.: Suicide and the Medical Community, Arch. Neurol. & Psychiat. 80:776, 1958.
2. National Offices of Vital Statistics, Washington, D. C.
3. Zilboorg, G.: Differential Diagnostic Types of Suicide, Arch. Neurol. & Psychiat. 35:270, 1936.
4. Robins, E., Gassner, S., Kayes, J., Wilkinson, R. H., and Murphy, G. E.: The Communication of Suicidal Intent, Am. J. Psychiat. 115:724, 1959.
5. Robins, E., Schmidt, E. H., and O'Neal, P.: Psychiatric Study of Attempted Suicide Over Sixty, A.M.A. Arch. Neurol. & Psychiat. 75:275, 1956.
6. Batchelor, I. R. C.: Attempted Suicide in Old Age, Brit. M. J. 2:1186, 1953.
7. Oliven, J. F.: The Suicidal Risk, New England J. Med. 245:488, 1951.
8. Sainsbury, P.: Suicide in the Middle and Later Years, (Paper presented at 5th International Gerontological Congress), San Francisco, 1960.
9. Schmidt, E. H., O'Neal, P., and Robins, E.: Evaluation of Suicide Attempts as Guide to Therapy, J.A.M.A. 155: 549, 1954.
10. Capstick, A: Recognition of Emotional Disturbance and the Prevention of Suicide, Brit. M. J. 1:1179, 1960.
11. Shneidman, E. S., and Farberow, N. L.: Clues to Suicide, Pub. Health Rep. 71:109, 1956.
12. Miller, M. H., Fellner, C. H., and Greenfield, N. S.: Depression, Suicide and Suicidal Gestures in Medical Practice, Ann. Int. Med. 51:78, 1959.

Discussion (Abstract)

Dr. E. H. Parsons, St. Louis, Mo. Dr. Schwartzberg has presented an interesting review of this age-old problem with which every psychiatrist is confronted repeatedly. He has reviewed comprehensively the literature on this subject and I am sure that several of us in this audience recall with amusement the late Dr. Gregory Zilboorg's comment which was, in effect, that he knew of no way of predicting the potential suicide. With no disrespect to Dr. Zilboorg, this is the only crack in his shield of omniscience of which I am aware. Dr. Schwartzberg has set up what might be termed indices of potential suicide utilizing the studies of Robins and his associates here in St. Louis, which indicated that slightly less than one half of those who commit suicide have previously verbalized such an intent. Adherence to his formula would screen in slightly less than half of the potential suicides. He is to be congratulated on this. There is validity in his insistence upon awareness of potential suicide by the psychiatrist particularly.

His recommendations as to the management of the suicidal attempt are certainly sound, and I would fully agree with his observation that the somatotherapy or chemotherapy commonly used is only a part or a step in the total treatment program required if one is to prevent a repetition of the suicidal attempt.

The matter of suicide among alcoholics was touched briefly by Dr. Schwartzberg. This is a point which I wish he had emphasized. In a study in the State of Missouri a few years ago by the Committee on Alcoholism of the Missouri State Medical Association, it was found that approximately 25% of the chronic alcoholics die by suicide. We have generally accepted the view of oral eroticism in the alcoholic. We have not, however, adequately studied the deeper meanings of the alcoholic who repeatedly drinks himself to oblivion. There are obviously certain physiologic phenomena which, from our point of view, "explain" the chronic alcoholic who draws what he terms "blanks," but the dynamics of the behavior pattern would seem to me to imply a rather distinct death wish evidenced in the return to Nirvana by way of alcohol. One may also speculate, with little hope of solution, upon the age-old question of whether we have been correct in our previous assumptions that all of mankind at all times is primarily concerned with self-preservation. If one examines such an hypothesis the ultimate conclusions become a bit absurd. Certainly all of us have been confronted with the patient who is as strongly motivated toward self-destruction as most of us are motivated toward self-preservation. I would wonder if one would not be inclined to agree with Zilboorg that suicide is not necessarily a behavioral component of depression. As a matter of fact, I believe in his study the suicide rate was higher among certain severe anxiety states than among the classical involutional melancholia group. Anhedonia cannot be directly correlated with suicidal drives. I would agree with Dr. Schwartzberg fully that we must keep the danger of self-destruction before us at all times and his check list technic or suggestions would certainly serve to raise a red danger flag in between 40 and 50% of the potential suicide cases. Many of us find a check list technic to be of value and certainly all of us use the equivalent of such a check list in our examination of any patient. I am inclined purely personally, however, to utilize what I like to think of as sensitive antennae, attempting to evaluate not only what the person says but who the person is and hope that the empathy of physician-patient relationship will allow the patient to express his sense of futility in his own words. Stated differently, I personally do not handle patients particularly well by a direct frontal type of verbal assault as it were.

I appreciate Dr. Schwartzberg's excellent review. It has caused me at least to review my own thinking in this aspect of practice and I am particularly indebted to him for his thoughtful, organized study of a part of practice which many of us dislike approaching directly, perhaps for clinically recognizable personal reasons. I would close with this reminiscence, if you will permit. Dr. Schwartzberg's suggestion of inquiring as to the state of the patient's spirits reminded me of the experience of my friend Dr. Frank Luton of Nashville, Tennessee, whom I had hoped to find present in this audience and who, shortly after his arrival at Vanderbilt, was attempting to instruct some of us in the technics of investigating the emotional status of the patient. The patient in this instance was a rather senile Tennessee hill-country man and when Dr. Luton said, "How are your spirits?", the old man cupped his hand to his ear and said, "Repeat that again, young feller." Upon Dr. Luton's repetition, he replied, "Hell, they're the best damn spirits in the whole county. I'll be glad to give you some if you want it, young feller." This, of course, was in the days of prohibition.

The Development and Management of Phobias*

MORGAN E. SCOTT, M.D., *Atlanta, Ga.*

The author has found group therapy of help in patients who have phobias and who have not responded to psychotherapy offered individually.

HIPPOCRATES[1] is credited with the first case report of a phobia. Other descriptive studies followed in the essay of John Locke.[2] Descriptions are also found in the writings of Kraepelin[3] and Oppenheim.[4] Both the latter attempted to explain the origin of phobias on a constitutional basis. Until Pierre Janet[5] submitted these reactions to appraisal there was little attempt to establish a psychologic basis for the origin of phobias. Janet compared phobias to hysteria and maintained that both prevented the individual from carrying out a task which was not pleasant—the hysteria by a motor or sensory limitation, the phobia by a panic reaction. Janet explained the fear as a result of the phobia. This concept added little to the understanding of the development of the phobia. Freud,[6] in 1895, formulated the first dynamic concept of phobias and his paper on "Obsessions and Phobias" opened up psychoanalytic studies of this neurosis. There was, for the first time, a differentiation of phobias from obsessions. The classical analytic dynamics of the phobia were described in a later paper, "Analysis of a Phobia in a Five-Year-Old Boy,"[7] published in 1909. Freud postulated the origin of the phobia in "Instinctual Striving with Fear of Punishment" or in his words, "castration fears." This fear was displaced on to an animal (horse) rather than the father as a less dangerous threat since the horse could be avoided more easily. The horse became a symbol for the father and displacement of the father fear to the horse fear was utilized. The original father fear could be repressed to emerge only if the symbol (horse) was encountered.

Fenichel[8] described several cases of phobias where there were few displacements. These cases consisted mainly of sexual phobias, fighting phobias and eating phobias. In other cases, he observed that the meaning of the fear is not apparent except through a long psychotherapeutic process. Even then the associations may only be inferred by the therapist.

Theory of Development

Phobias have been called "The Neurosis of Children." In human adaptation with its prolonged period of dependency there are fears in every infant related to the actual inability to meet environmental demands. As the child grows, the manner in which new situations are managed results in either the mastery of fear or its continuance. Parents who are fearful are likely to induce fear in the child or to fail to provide the child with support needed to overcome fear. Ridicule, derision or overprotection, likewise, lead to poor adaptive mechanisms in the child with resultant fear. Fear is a response to danger.[9] It is understandable then where danger is over-emphasized, fear is also over-emphasized. Fear leads to a fall in self-esteem with further accentuation of fear.[9]

Often the phobia is established by nonverbal behavior (an example is Case 4, where the mother would mention sex with clinched teeth and communicated by nonverbal means her own feelings about sex to the daughter).

Although many cases derive from sexual or aggressive impulses that are blocked by the environment, other impulses such as the need for social participation, or the need for competitive sports are equally common. Rather than limiting our concept to the danger of castration, we can generalize that fear may arise from any situation which is perceived as a danger.

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In cases where there is symbolic displacement, what factors determine the object or situation to which the phobia is displaced? This determination is based on one of two principles, the principle of contagion or the principle of similarities. Contagion implies the events, situations or objects present at the original trauma may become symbolized. For example, *H.*, a 10 year old boy, was masturbating in his bedroom. It was raining outside and thundering. The mother came in to lower the window, caught him and punished him. Thereafter *H.* was afraid of rainstorms and thunder.

Situations or objects which resemble the original trauma also become phobia symbols. *G.*, a 13 year old boy, experienced a sodomy attack by a man. Thereafter he was phobic about enemas and suppositories. The similarity here seems obvious.

The Management of Phobias

Psychoanalytic therapy in its classical application was found to fail in Freud's experience[10] with treating phobias. He stressed the importance of exposing the patient to the feared object or situation. Positive transference in these situations served as a support for the patient and assisted in controlling the intense fear. Perhaps, with this modification in technic, psychoanalysis is the treatment of choice in phobics.

Hypnosis may serve as a temporary expedient or may actually be successful in some cases. Spiegel recently, in a lecture, described a case of animal phobia where the hypnotic technic was used successfully. However, with a severe neurosis such as the cases described in this article, only an experienced well-trained hypnotist would be able to decide if such treatment would be advisable.

Chemotherapy (tranquilizers) has been widely used in phobic neuroses, but definitive results have not been obtained in my experience. For those interested, I am sure the literature contains ample references.

Individual (nonanalytic) psychotherapy, both of supportive and interpretative variety, is successful in some cases where the phobia is near consciousness. Likewise, the chronicity of the phobia seems to determine the outlook with this therapy.

During the past year, several patients with phobias have been followed by the Department of Psychiatry. These patients had failed to respond to psychotherapy. Group therapy was decided upon as the method of choice. According to the experience of Furst[11] and Powdermaker,[12] the members of the group should be sufficiently varied to give a number of issues and sufficiently similar to give each other support. At the beginning there was some concern on my part about placing patients with phobic symptoms in a group. However, this similarity has not been a detriment to group progress at this point. This group meets once weekly in one and one-half hour sessions. It is composed of 6 members at present with 7 in the original meetings—one member dropped out because of transportation difficulties (she lived 100 miles away). Five of the members came from Greater Atlanta, one from a town over 200 miles away, traveling to and from meetings by plane. Average attendance has been over 70 per cent. All members are women ranging in age from 24 to 44 years of age.

In addition to the members and the leader, a recorder is present at the meetings and functions as a silent member and observer.

The technic used in this group is based on principles defined by Frank and Powdermaker in their discussion on the processes of (group) therapy.[13,14] A continual attempt is made by the leader to focus on the group and not on individuals. The group purpose is to attain a level of cohesiveness where mutual analysis is promoted. Group feelings are explored and topics which are presented to the group are continually subjected to group interpretation.

In each of the 6 cases individual psychotherapy had not been successful in relieving the phobia; 3 patients (Cases 1, 3 and 4) were treated by other psychiatrists, the others were previously treated by me in individual psychotherapy. A 6 month minimum of individual therapy without progress is the criterion used as lack of success. As has been the experience of other therapists, phobics are frequently childlike (immature) with parentification of the therapist and the craving for magic.[8] Frequently an overdependence on the therapist hampers progress. In a group situation the dependence on the therapist is limited.

Case 1. (Phobic Neurosis). J.H., a 36 year old woman, had been seen in individual psychotherapy for 6 years because of an increase in her fear of being

alone. This fear had increased until it was no longer possible for her husband to leave her to go to work. She was first hospitalized for 5 weeks, introduced into the group and then continued in the group as an outpatient. During the past 5 months she has made slow but steady progress. The group has given her support in her attempts to remain alone. She now drives distances alone up to two miles and recently has been able to stay alone while her husband was on a business trip. When first seen the patient had no insight into her phobia, but stated, "I am afraid of panic." The group has helped her explore some of the origins of her fear as it related to her alcoholic father who left her alone frequently. Furthermore, the precipitation of her fear as an adult has also come up in the group (the death of her first husband). She frequently discusses her feelings about her present husband and the similarities to her feelings about her father.

Case 2. A.G. is a phobic 35 year old white woman. She first was treated on an individual basis for 6 months without resolution of her phobias for crowds and leaving home. She also had an intense fear of hurting her children and of losing control of herself. Because of her fears it was not possible for her to leave home or for her to be with her children without another adult. With group therapy she has become aware that her phobic symptoms represent a displacement of her anger toward her father (who was a severe alcoholic). She is now driving alone and is able to care for her children. She is able to attend church and other group meetings.

Case 3. E.A., a 44 year old white woman, was intensely fearful of fire trucks, fires, and pregnant women. Since she is a nurse this phobia about pregnant women impaired her work, leading to financial distress. These symptoms had been present to a marked degree for 4 years, although fear of fires seems always to have possessed her. After 18 months of individual therapy without progress she was placed in the group. In the group she has become aware that the onset of her symptoms seems to have related to the 3 stillborn babies she had had. Following this realization she went through a period of depression and then was able to return to work as a nurse. It is interesting that she now works for an obstetrician. Her fear of fire trucks remains but is not disabling to her.

Case 4. N.G., a 30 year old housewife, received psychotherapy for 2 years for phobic symptoms without relief. Her main complaints were fear of pregnancy and fear of being alone. These symptoms had been present for about 4 years and had led to increasing marital difficulties. Despite her intellectual understanding of her problem, she continued to have marked fear when alone or when intercourse was anticipated. She now submits to intercourse although she is frigid. She remains alone although she checks to see if the neighbors are home ("I depend on them as I do other group members.").

Although each member of the group has made some progress, no implication is made that this method of treatment offers any panacea for all cases. However, its economy, promotion of mutual analysis, and support all make this method of treatment a consideration in these difficult cases. It seems to be beneficial in some cases where individual therapy has failed. A longer period of trial and further exploration of the usefulness of this therapy in these cases is definitely indicated.

Summary

A brief historical outline of the study of phobia is presented. The Freudian theory of phobia is also presented. Recent theories based on adaptational studies are outlined. The various types of treatment of phobias are discussed with a discussion of group therapy as used in phobic cases.

References

1. Hippocrates: On Epidemics, V Section LXXXII.
2. Locke, J.: An Essay Concerning Human Understanding, in St. John, J.A. (Ed.), The Philosophical Works of John Locke, London, G. Bell, 1913.
3. Kraepelin, E.: Lehrbuck der Psychiatrie. 7th ed. Barth, Leipzig, 1903.
4. Oppenheim, H.: Textbook of Nervous Disease for Physicians and Students. 5th ed. Schulze, Edinburgh; Stechert, New York, 1911.
5. Janet, P.: Les nevroses, Bibliotheque de Philosophie, Paris, 1909.
6. Freud, S. (1895): Obsessions and Phobias: Their Psychic Mechanisms and Their Aetiology, in Collected Papers, Vol. 1, pp. 128-37, Basic, New York, 1959.
7. Freud, S. (1909): Analysis of a Phobia in a Five-Year-Old Boy, in Collected Papers, Vol. 3, pp. 149-289, Basic, New York, 1959.
8. Fenichel, O.: The Psychoanalytic Theory of Neurosis. Norton, New York, 1945.
9. Rado: Psychoanalysis of Behavior. Grune & Stratton, Inc., New York, 1956, pp. 222 and 243.
10. Freud, S. (1919): Turnings in the Ways of Psychoanalytic Therapy, Collected Papers, Vol. 2, pp. 392-402, Basic, New York, 1959.
11. Furst, W.: Homogenous versus Heterogeneous Groups, Internat. J. Group Psychotherapy 1:120, 1951.
12. Frank, J. D.: Group Psychotherapy, Am. Hand. Psych. Vol. II, Chap. 67, Basic, New York, 1959.
13. Ezriel, H.: A Psychoanalytic Approval to Group Therapy, Brit. M.J. Psychol. 23:59, 1950.
14. Sutherland, J. D.: Notes on Psychoanalytic Group Therapy, Psychiatry 15:111, 1952.

Discussion (Abstract)

Dr. William G. Reese, Little Rock, Ark. The title of this interesting paper is somewhat misleading in designating "management of phobias," but this is corrected by the context of the paper in which Dr. Scott makes it clear that one treats *patients* with phobias rather than treating phobias. He emphasizes the individuality of patients with phobias, indicating that such patients present different levels of emotional maturity, different degrees of ego strength and, in fact, different combinations of symptoms. In my experience, and I suspect in yours, one rarely sees patients with only phobic symptoms. Free-floating anxiety or depression is often present, even when the phobic situation is avoided, and symptoms of obsession and compulsion are usually present to some degree. In fact, several psychiatrists consider the phobic-obsessive-compulsive category to be the appropriate diagnostic entity. Conversion features and dissociative symptoms often occur in patients with prominent phobias.

Concerning the genesis of phobias the author indicates, without emphasis, the relevance of the patient's interpersonal relationships, particularly with significant persons. Thinking in terms of the mechanistic

formula that a blocked impulse produces anxiety plus repression, one may lose sight of the importance of the interpersonal experiences in the genesis of the phobia or of other psychopathologic manifestation. If I might distort the Judeo-Christian myth of creation as an example, we might speculate that Eve developed a snake phobia by the process of repressing her sexual desires and substituting by displacement the snake as a phobic object. This formulation might divert us from Eve's central concern over the possible loss of parental love and protection. I am only restating the author's position concerning the genetic importance of interpersonal factors in the attempt to emphasize the hazard of mechanical use of a mechanical model.

I have attempted to enlarge our field of observation in order to bring into perspective the therapeutic tasks and methods.

The author specifically demonstrates the usefulness of group psychotherapy in the treatment of *persons* (not conditions) who are immature and chronically phobic. Perhaps the desirability of the group situation emphasizes the interpersonal aspects of the maladjustments.

Frank and Ascher (Corrective Emotional Experience in Group Therapy, Am. J. Psychiat. 108:126, 1951.) have contrasted individual and group therapy by pointing out that: (1) in the group situation dependence on the therapist is diluted by the opportunity for dependence upon other members of the group; (2) opportunities to stimulate significant emotional reactions are more likely in the group since this constitutes a more realistic social situation in which problems on rivalry, status struggles and a wider range of transference objects is available; and (3) reality testing is facilitated in the more nearly *real* situation of group interaction; with all of these factors being conducive to corrective emotional experiences.

I would like to ask Dr. Scott to amplify his remarks concerning the factors which he found to make group therapy particularly effective with the type of patients he described.

Dr. Scott (Closing). Dr. Reese has certainly emphasized a point which I may have left unclear; namely that interpersonal factors are of primary importance in the production, prevention, and resolution of phobias. In producing the phobia, important people in the subject's life are of key importance in initiating the use of phobic devices. In prevention and resolution there certainly is a similar importance. The therapeutic use of transference and its counterpart in childhood is one example of interpersonal relationship.

Group efficacy in phobia depends on the strong group transference with dependency developed on the total group rather than on the therapist alone. Actual instances of improved interpersonal relationship, improved social relationships and greater social participation in other group activities result from successful group therapy. Overdependency is diminished since there is sharing in the group transference.

Clinical Usefulness of Determining Bromsulphalein and Its Metabolic Products: Preliminary Observations*

GABRIEL L. PLAA, Ph.D., ROBERT D. SPARKS, M.D., JOHN K. ABIDE, M.D., and FRED M. HUNTER, M.D.,† *New Orleans, La.*

It appears that the mechanism for the clearance of bromsulphalein is probably more than hepatic uptake, storage and excretion. The conjugation of the dye is apparently part of the function involved and there may be significance of its relationship to storage. More studies will be needed relative to the conjugates of the dye, their storage and excretion.

SULFOBROMOPHTHALEIN (BSP.) is a phthalein dye excreted primarily by the liver.[1] Rosenthal and White[2] detected hepatic dysfunction by estimating concentrations of BSP. in serum at timed intervals after intravenous administration of a standard dose of the dye. Cantarow and Wirts[3] believed that this clearance depended upon initial rapid accumulation of BSP. chiefly in hepatic parenchymal cells and a rate-limited transfer into bile. The first evidence of hepatic alteration of BSP. was indicated by Brauer, Krebs and Pessotti.[4] They demonstrated that BSP. was excreted into bile in colorimetrically similar but chromatographically different fractions. Four bands containing BSP. were separated from rat bile by adsorption on alumina columns.[5] Grodsky, Carbone and Fanska[6] fractionated BSP. in human bile by using paper chromatography. Both groups found that only one fraction had colorimetric and chromatographic characteristics of unconjugated BSP. The remaining fractions have been shown to be conjugates of BSP. with amino acids.[6-8]

Estimation of concentrations of unconjugated BSP. (U-BSP.) and conjugated BSP. (C-BSP.) in serum yields more information than that gained from the standard colorimetric estimation of total BSP.[9,10] To date, separation and estimation of these concentrations has depended on alumina column or paper chromatographic systems. Both methods are technically impractical for clinical laboratories.

Thomas and Plaa[11] observed that sulfobromophthalein and its major conjugates partitioned differently in certain aqueous-organic solvent systems. They employed these characteristics in the development of a method for rapid estimation of U-BSP. and C-BSP. in blood. This paper reports our experience with this procedure in 31 patients with liver disease and in 15 normal subjects.

Methods

Each subject was examined for historical, physical or biochemical evidence of hepatic disease. Fifteen normal and 31 abnormal patients were studied. The abnormal patients were selected to represent the following hepatic diseases: hepatitis, congestive heart failure, portal cirrhosis and carcinoma metastatic to the liver. Histologic confirmation of the hepatic disease was obtained in 16 of the 31 abnormal patients. The diagnoses in the remaining 15 abnormal subjects were established from clinical evidence.

Sulfobromophthalein sodium, 5 mg. per kilogram of measured body weight, was given intravenously while the patients were in a fasting and resting state. Samples of peripheral venous blood were drawn 15, 30, and 45 minutes after the BSP. was given and allowed to clot at room temperature.

Concentrations of U-BSP. and C-BSP. were estimated by the method of Thomas and

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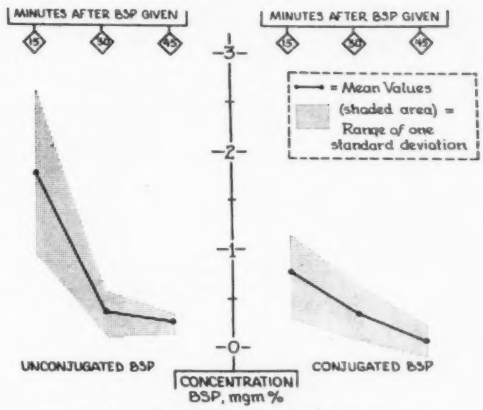
Plaa.[11] In this method total BSP. (U-BSP. + C-BSP.) was first estimated; then an estimation was made of that fraction of the total BSP. which is extractable by a butanol-ether solvent system. This extractable BSP. represents 77% of the U-BSP. and 25% of the C-BSP. present in the original serum. From a set of simultaneous equations the concentrations of U-BSP. and C-BSP. in the original serum were calculated. The absorbance reading of each solution was obtained in 12 mm. cuvettes on a Coleman Jr. Spectrophotometer, using a wave length of 580 millimicrons. The results were expressed in milligrams of BSP. per 100 milliliters of serum. A 5.0 mg.% solution of BSP. is equivalent to a 50% retention of BSP. An individual with a total BSP. retention greater than 5% at 45 minutes was considered to be abnormal.

Results

The data obtained from the 16 normal subjects are reported in table 1. The mean concentrations of U-BSP. and C-BSP. in serum at 15, 30, and 45 minutes after the administration of BSP. are graphically demonstrated in figure 1. The range of the standard deviation at each point is indicated. These values are quite similar to those of Carbone, Grodsky and Hjelte.[10]

The results from the subjects having hepatic disease are grouped according to the phase of the disease (Table 2). The total BSP. concentrations (U-BSP. + C-BSP.) at 45 minutes are abnormally high in all instances, indicating hepatic dysfunction. The serial estimations demonstrate widely varying and overlapping patterns within each group. However, four general patterns of C-BSP.

FIG. 1



Estimations of U-BSP and C-BSP in Serum.
16 Normal Subjects
(mean plus one standard deviation)

TABLE 1

RESULTS OF ESTIMATIONS OF C-BSP. AND U-BSP. CONCENTRATIONS IN SERUM FROM NORMAL SUBJECTS

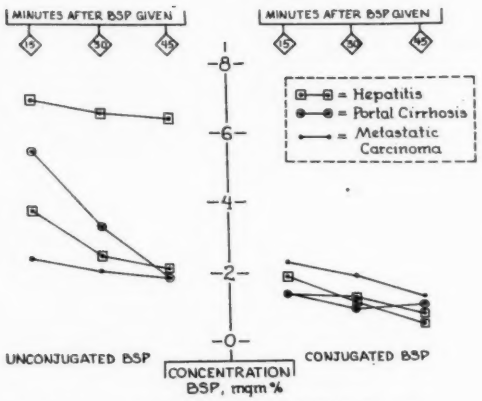
Subject No.	U-BSP. (mg. %) 15'	30'	45'	C-BSP. (mg. %) 15'	30'	45'
1	2.60	.20	.20	1.00	.30	0
2	2.60	.20	.15	1.60	1.00	.30
3	3.00	.80	.40	.75	0	0
4	.60	.50	.20	.80	.10	.10
5	1.80	.30	.30	.15	.10	.05
6	2.46	.59	.34	.98	.45	0
7	1.28	.09	.17	.62	.26	0
8	.74	.17	.17	.98	.52	0
9	.82	.19	.09	.36	0	0
10	1.77	.34	0	.75	.15	.30
11	.98	.15	.10	.35	.09	0
12	2.60	.17	.14	1.60	1.00	.26
13	.62	.43	.17	.76	.74	.11
14	2.22	.36	.40	0	.24	0
15	2.60	.14	.20	1.00	.26	0
Mean	1.79	.34	.22	.74	.34	.08
Standard deviation	.81	.23	.10	.45	.30	.12

TABLE 2

RESULTS OF ESTIMATIONS OF U-BSP. AND C-BSP. IN ABNORMAL SUBJECTS

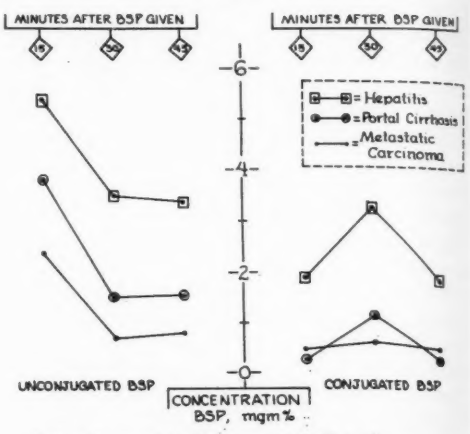
Subject No.	U-BSP. (mg. %) 15'	30'	45'	C-BSP. (mg. %) 15'	30'	45'	C-BSP. Pattern
			Hepatitis, Acute Phase				
16	4.80	4.40	3.60	0	0	0	D
17	7.00	6.50	6.40	1.40	1.20	.75	A
			Hepatitis, Early Recovery Phase				
18	4.04	4.49	3.40	2.33	.33	.33	A
19	4.70	4.00	3.00	0	0	.50	B
20	3.80	2.63	2.12	1.98	1.11	.54	A
			Hepatitis, Late Recovery Phase				
21	5.30	3.30	3.20	1.90	3.20	1.80	C
22	1.83	.34	.34	.14	.05	.05	N
23	3.71	.61	.30	0	.13	0	N
24	5.81	4.14	2.15	.87	0	.06	N
25	4.10	2.40	1.10	.40	.40	1.10	B
			Congestive Heart Failure, Acute				
26	5.20	4.20	3.20	0	0	0	D
27	7.10	7.00	6.10	1.55	.69	1.10	?
28	10.00	8.20	7.40	0	0	0	D
			Congestive Heart Failure, Chronic				
29	6.90	.51	.31	0	.50	.29	C
30	5.10	3.10	1.90	1.55	.69	1.30	?
31	5.65	4.80	.90	0	.69	2.00	B
			Portal Cirrhosis, With Portal Hypertension				
32	3.10	2.00	2.00	2.70	1.40	.22	A
33	3.90	1.60	1.67	.30	1.20	.34	C
34	3.80	1.40	.74	0	.36	.46	B
35	5.30	4.00	3.00	.71	.85	1.20	B
36	5.50	3.30	1.90	1.40	1.00	.99	A
			Portal Cirrhosis, No Portal Hypertension				
37	3.10	2.60	2.50	3.60	2.40	1.90	A
38	2.80	1.50	1.20	.46	.62	.63	B
39	1.60	.60	.60	.34	0	0	N
			Metastatic Carcinoma				
40	2.50	.70	.80	.50	.70	.40	C
41	8.70	6.70	5.20	0	0	0	D
42	2.60	1.30	.90	.05	.10	.30	B
43	2.60	2.10	1.90	2.25	1.90	1.20	A
44	3.90	2.10	1.30	1.20	1.70	1.70	B
45	3.90	1.50	1.70	.70	.73	.30	C
46	1.99	1.56	1.08	0	0	.33	B

FIG. 2



Estimations of U-BSP and C-BSP in Serum.
PATTERN A

FIG. 4



Estimations of U-BSP and C-BSP in Serum.
PATTERN C

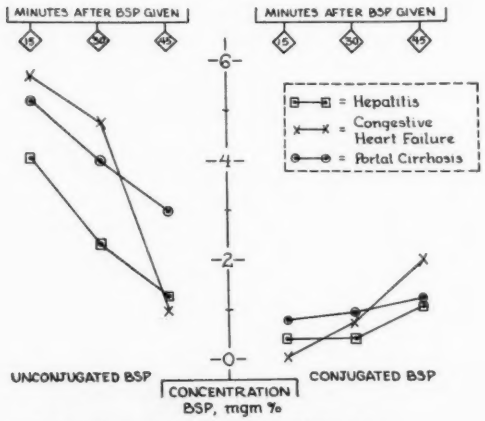
concentrations are observed and are represented in figures 2-5.

Pattern A. Elevated but decreasing concentrations of C-BSP. (Fig. 2): Three patients with hepatitis, 3 with portal cirrhosis, and 1 with carcinoma metastatic to the liver had abnormally high concentrations of C-BSP. in each sample of serum. The concentrations progressively decreased as the interval of time after the administration of BSP. increased; however, the slopes of these curves are very similar to the pattern of the mean values in normal subjects.

Pattern B. Increasing C-BSP. concentrations (Fig. 3): Two patients with hepatitis, 1 with congestive heart failure, 3 with portal cirrhosis and 3 with metastatic carcinoma demonstrated serum C-BSP. concentrations that progressively increased with time. In only 3 of these 9 subjects were the concentrations at 15 and 30 minutes definitely abnormal, but the slope of the curves and the 45 minute values in all 9 subjects were strikingly abnormal.

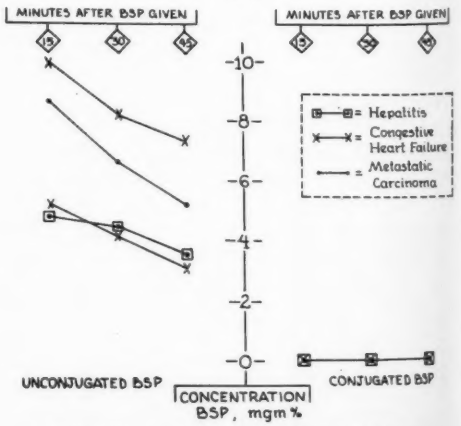
Pattern C. Highest C-BSP. concentration at 30 minutes (Fig. 4): One patient with hepatitis, 1 with congestive heart failure, 1 with portal cirrhosis and 2 with metastatic carcinoma demonstrated C-BSP. concentra-

FIG. 3



Estimations of U-BSP and C-BSP in Serum.
PATTERN B

FIG. 5



Estimations of U-BSP and C-BSP in Serum.
PATTERN D

tions that were greater than normal in the samples of serum obtained either at 30 or 45 minutes; the higher value occurred in the 30 minute specimen.

Pattern D. No C-BSP. in the 3 samples (Fig. 5): No C-BSP. was detected by the differential extraction method in each sample of serum from 4 subjects. One patient had hepatitis, 2 congestive heart failure and the other, carcinoma metastatic to the liver.

Discussion

Until recently, the clearance mechanism for BSP. was considered to consist of hepatic uptake, storage and excretion into bile. [12,13] The discovery of altered BSP. in bile[4] suggested a metabolic phase. Combes and Stakelum[7] examined three metabolic products of BSP. in rat bile and found each was conjugated with the amino acid constituents of glutathione through a thio-ether linkage with cysteine. Conjugates of BSP. appear in serum of normal subjects[10] and experimental animals.[14] The slopes of the C-BSP. curves observed in normal rats and humans are parallel from 15 through 45 minutes. The peak concentration occurs at approximately 15 minutes.

The appearance of C-BSP. in the serum of normal subjects has not been explained. One might speculate, however, that its concentration in the serum reflects the balance between conjugation of BSP. and storage and excretion of these conjugates.

In Pattern A (Fig. 2), the concentration of C-BSP. progressively decreased as is seen in the normal pattern but the concentrations are abnormally high at each interval. In these individuals conjugation of BSP. apparently occurs at a rate which exceeds storage and excretion of these products. Nevertheless, the rate of excretion prevents increasing amounts of C-BSP. from appearing in the serum.

Pattern B (Fig. 3) demonstrates data from subjects who had increasing concentrations of C-BSP. The estimations at 15 minutes were within the range of normal, indicating that the balance between conjugation of BSP. and excretion of the conjugates was normal. However, at 30 and 45 minutes, increasing amounts of C-BSP. appeared in the serum, indicating that the rate of conjugation now exceeded storage and excretion.

In Pattern C (Fig. 4) the highest concentration of C-BSP. occurred at 30 minutes. This would indicate that initially the rate of conjugation exceeded storage and excretion of C-BSP. After the 30 minute interval, however, storage and excretion of C-BSP. exceeded conjugation.

Examination of Patterns A, B, and C suggests that these represent a delay in the development of the C-BSP. pattern seen in normal individuals. The C-BSP. curve observed during 45 minutes in Pattern B may reflect a sequence of events which occurs in normal subjects in about 15 minutes. Similarly the initial ascent of the curve in Pattern C may reflect a prolongation of the initial ascent of the normal curve. However, the subsequent descent in Pattern C tends to parallel the descent of the normal curve. Thus, Pattern C more closely approximates the normal time-concentration curves for C-BSP. than does Pattern B and therefore appears less abnormal than Pattern B. Finally, Pattern A seems to reflect a delay in the descent of the curve. For this reason, Pattern A seems to be the least abnormal of the three curves.

Pattern D (Fig. 5) was found in 4 subjects. C-BSP. at no time appeared in serum. This suggests that either no conjugation of BSP. occurred or storage and excretion of C-BSP. equalled the rate of its formation.

These interpretations are speculative. The final interpretation of these patterns will depend upon studies that measure excretion and tissue storage of these conjugates.

Summary

1. Estimations of U-BSP. and C-BSP. in serum at 15, 30 and 45 minutes after BSP. administration do not produce patterns that are diagnostic for a specific type of hepatic disease.

2. The precise significance of the serum concentrations of U-BSP. and C-BSP. has not been determined. However, four general types of abnormal serum patterns for C-BSP. have been described. These patterns probably reflect the relationship between the rate of production of C-BSP. and the storage and excretion of the conjugates.

References

1. Rosenthal, S. M., and White, E. C.: Studies in Hepatic Function, J. Pharmacol. & Exper. Therap. 24:265, 1924.
2. Rosenthal, S. M., and White, E. C.: Clinical Application

of the Bromsulphalein Test for Hepatic Function, J.A.M.A. 84:1112, 1925.

3. Cantarow, A., and Wirts, C. W.: Excretion of Bromsulfalein in the Bile, Proc. Soc. Exper. Biol. & Med. 47:252, 1941.
4. Brauer, R. W., Krebs, S. J., and Pessotti, R. D.: Bromsullonphthalein as a Tool for Study of Liver Physiology, Fed. Proc. 9:259, 1950.
5. Krebs, J. S., and Brauer, R. W.: Metabolism of Sulfobromophthalein (BSP) in Rat, Am. J. Physiol. 194:37, 1958.
6. Grodsky, G. M., Carbone, J. V., and Fanska, R.: Metabolism of Sulphobromophthalein, Nature 183:469, 1959.
7. Combes, B., and Stakelum, G. S.: Conjugation of Sulfobromophthalein Sodium with Gluthathione in Thio-ether Linkage by Rat, J. Clin. Invest. 39:1214, 1960.
8. Meltzer, J. I., Wheeler, H. O., and Cranston, W. I.: Metabolism of Sulfobromophthalein Sodium (BSP) in Dog and Man, Proc. Soc. Exper. Biol. & Med. 100:170, 1959.
9. Higgins, F. E., Foulk, W. T., and Bollman, J. B.: Column Chromatography of Bile, Serum and Urine After Intravenous Administration of Sulfobromophthalein, Gastroenterology 38:194, 1960.
10. Carbone, J. V., Grodsky, G. M., and Hjelte, V.: Effect of Hepatic Dysfunction on Circulating Levels of Sulfobromophthalein and Its Metabolites, J. Clin. Invest. 38:1989, 1959.
11. Thomas, M. C., and Plaa, G. L.: A Method for the Simultaneous Determination of Sulfobromophthalein Sodium (BSP) and Its Major Metabolite in Blood, Am. J. Clin. Path. 34:488, 1960.
12. Brauer, R. W.: Liver Function, Pub. AIBS, Washington, D. C., 1958.
13. Popper, H., and Schaffner, F.: Liver Structure and Function. New York, McGraw-Hill Book Company, Inc., 1957.
14. Krebs, J. S.: Relation of the Metabolism of Sulfobromophthalein Sodium to Its Blood Clearance in the Rat, Am. J. Physiol. 197:292, 1959.

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Evaluation of Methatar in Eczema

LOUIS J. WISE, JR., M.D., *Jackson, Miss.*, and
VINCENT J. DERBES, M.D.,† *New Orleans, La.*

METHATAR* is a water-washable, oil-and-water emulsion containing 5% liquor carbonis detergens, 0.2% benzethonium chloride, d, l-methionine, and a protein hydrolysate (composed of l-leucine, l-isoleucine, l-methionine, l-phenylalanine, and l-tyrosine). The preparation combines the anti-eczematous qualities of tar with the antibacterial activity of benzethonium chloride. The amino acid mixture is proposed to have an antipruritic character and a stimulating effect on tissue regeneration.[1]

Materials and Methods

One hundred and one unselected patients with various dermatitides were treated with Methatar. An additional 13 patients were selected with symmetric dermatitis; and the preparation was compared to a 1% hydrocortisone, 0.2% benzethonium chloride combination.

The Methatar cream was dispensed in the Charity Hospital clinic; and on subsequent visits the degree of improvement was recorded as excellent (E), moderate (M), slight (S), or failure (F). For convenience of reporting, the cases are grouped into general diagnostic categories (Table 1).

In table 2 the comparison study is similarly recorded. These patients were selected with bilaterally, symmetrical lesions and hospitalized for better control. The third column of table 2 lists the preparation considered more beneficial by the patients.

Results

In the pyodermas and secondarily infected dermatoses, the best results were obtained with the superficial infections; whereas, the ecthymatous lesions tended to be more resistant.

TABLE 1

CASES TREATED WITH METHATAR

Diagnosis	*E*	*M*	*S*	*F*	*Total*
Pyoderma	13	7	6	4	30
Atopic dermatitis	3	9	4	3	19
Contact dermatitis	7	2	1		10
Infectious eczematous dermatitis	5	4	1	5	15
Lichen simplex		7	1	1	9
Hand eczema	3	1	4		8
Nummular eczema	1	2	3		6
Seborrheic dermatitis	2	1			3
Stasis eczema				1	1

E = excellent; M = moderate; S = slight; F = failure.

The various types of dermatitis were more unpredictable in their responsiveness. Acute contact dermatitis and seborrhea yielded best to therapy. The cases of lichen simplex chronicus, atopic dermatitis, and nummular eczema were more stubborn, as would be expected.

The first two columns of table 2 represent the observers' impression of the response to treatment, and column three presents the patient's preference. The over-all results were better in this group of patients since they were hospitalized and treated under controlled conditions with enforced bed rest. The rate and degree of improvement was approximately the same in affections treated with hydrocortisone and those treated with Methatar. The majority of patients, however, thought that their symptoms were relieved better by the hydrocortisone preparation.

In this study only 6 patients complained of irritation to Methatar and showed a definite exacerbation of their dermatitis.

Summary

One hundred and one cases of dermatitis were treated with Methatar. Eighty-seven cases were improved. The response was best in acute forms of dermatitis and superficial bacterial infections. The chronic forms of dermatitis showed lesser degrees of improvement.

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*Trademark of The Borden Company.

TABLE 2

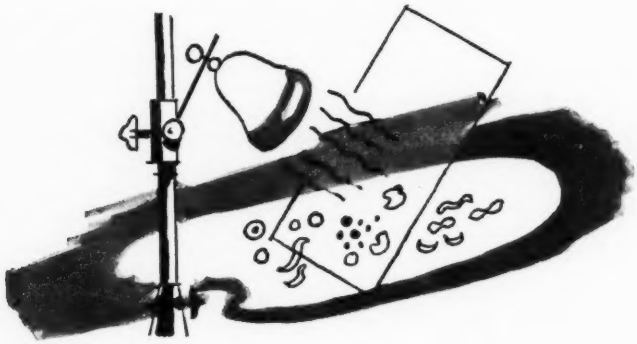
COMPARISON OF METHATAR AND HYDROCORTISONE

Cases	*Left Side Hydrocortisone*	*Right Side Methatar*	*Patient's Preference*
1. Contact dermatitis	E	E	No preference
2. Contact dermatitis	E	E	No preference
3. Contact dermatitis	E	E	Hydrocortisone
4. Contact dermatitis	E	E	Hydrocortisone
5. Contact dermatitis	E	M	Hydrocortisone
6. Infectious eczematous dermatitis	M	M	Hydrocortisone
7. Infectious eczematous dermatitis	E	E	Hydrocortisone
8. Nummular eczema	M	M	No preference
9. Nummular eczema	M	S	Hydrocortisone
10. Hand eczema	E	E	Hydrocortisone
11. Hand eczema	S	S	Methatar
12. Hand eczema	S	S	No preference
13. Atopic dermatitis	M	M	No preference

Methatar was compared to a hydrocortisone cream in 13 patients with symmetrical dermatitis. Although most of the patients thought hydrocortisone best relieved their symptoms, objectively there was little difference between the hydrocortisone cream and Methatar.

Reference

1. Levine, Albert J., Davis, Oscar F., Horwitz, Bernard, Sloan, Noah, and Beck, Charles: Influence of Amino Acid Therapy in Chronic Idiopathic Pruritus Ani, Gastroenterology 35:409, 1958.



The President's Page

Appearing in the August 5 issue of the *Saturday Evening Post* was an article entitled "Can We Get Rid of Bad Doctors" by Milton Silverman. Overlooking the fact that the display of the title in red letters on the cover no doubt caused a number of "spot readers" to, without bothering to read the article itself, mutter . . . These Damn Doctors, the article points out a number of cases of "bad doctors" and did emphasize that the profession itself on all levels is taking steps to eliminate those isolated cases of violations of the Hippocratic Oath and the Professions' Code of Ethics.

This article, with its examples and statistics, adds veracity to an observation I have made each time the matter of the "Few Bad Apples in the Barrel" comes up and that is, in a great majority of such cases, the cause is professional incompetency. This primary cause may be overshadowed, but nevertheless is there. Causes given for the revocation of most licenses is violation of narcotic laws and illegal procedures. A thorough investigation of these cases would no doubt bear out my contention that professional incompetency was the underlying factor causing the individual to resort to the violation or illegal procedure leading to license revocation. If the above hypothesis be true, this situation is most appalling. In no other profession is more opportunity provided to maintain proficiency than in medicine. The May 1961 issue of *New Medical Materia* cited figures showing two teachers for each medical student. Medical publications number in the thousands and never a day goes by but what the physician has an opportunity to attend a medical meeting.

While it is not within the scope of its operation for the Southern Medical Association to function as a disciplinary body, this organization through the publication of the *Southern Medical Journal* and annual meetings makes available to physicians means of maintaining competency in their profession. This year in Dallas, November 6-9, the 55th Annual Meeting of the Association will be held with the Dallas and Tarrant County Medical Societies as co-hosts. At this meeting will be presented papers and exhibits covering every aspect of medical and surgical practice. The twenty-one scientific Sections will present 52 half-day sessions. Four symposia on timely subjects will be held, and numerous scientific and technical exhibits will present the latest methods, technics and results of research projects. In addition, the social functions of the Association, the Sections, the alumni and fraternal groups and the organizations meeting conjointly will offer an excellent opportunity for the interchange of ideas and thoughts and for the renewal of old acquaintances. As physicians we received excellent training in medical school; however, our field is such that our education is never complete. Let all of us as individuals make sure that we are never guilty of professional incompetence. Let us also assume the responsibility of seeing that our confreres also maintain their proficiency by urging participation in the excellent programs of continued education available.

A hotel accommodation application form appears on page 1037. Complete this form and mail today and join me and thousands of other physicians in Dallas in November.

Sincerely,

LEE F. TURLINGTON, M.D.
President

EDITORIALS

TOTAL APLASTIC ANEMIA AND OTHER COMPLICATIONS FOLLOWING THE SO-CALLED "ANTITHYROID DRUGS" IN THE TREATMENT OF THYROTOXICOSIS

In no disease, perhaps, is the treatment less stereotyped or uniform than in cases of severe hyperthyroidism or exophthalmic goiter. Each case is a law unto itself and should be studied in every detail from the clinical, laboratory, and in a large number, from the sociologic standpoint. Each patient presents an individual problem modified by many subsidiary facts, and the type of treatment to be instituted must be elastic and adaptable to every variety of case. It is now conceded that the most efficacious method of treating hyperthyroidism is one which combines both medical and surgical measures. Alone, either will be found inadequate for the great majority of cases. They call for the constant and closest cooperation between the internist and the surgeon from the very beginning of the treatment, so the clinical course will be completely familiar to both. Unfortunately, although such close cooperation between the internist and surgeon prevailed during the era when iodine in the form of Lugol's solution constituted the recognized preoperative preparation, since the advent of the so-called antithyroid drugs and radioactive iodine the management of the treatment of hyperthyroidism has been taken over almost exclusively by the internist. Not only does the surgeon fail to see the patient before medicinal therapy has begun, but also he sees only the patient in whom medicinal therapy has been unsuccessful or in whom complications due to the antithyroid drugs have ensued.

Response to antithyroid medicinal therapy in an adenomatous goiter is even less predictable than in Graves' disease. In the latter a permanent remission after discontinuance of the drug will occur in less than half of the patients, even though they were under the continuous administration of the drug for 2 and often 3 years. More than half of the cases suffer exacerbation of the signs and symptoms of the disease upon discontinuance of the antithyroid drugs. In the adenomatous goiter with hyperthyroidism the failure to maintain a permanent remission is well over 75 per cent. It is to be noted that in the medically treated patients who are not in a permanent remission, the disease process has continued and unknown damage to the patient may have been incurred.

Even in the event of a euthyroid state, which can only be maintained by the continuous use of an antithyroid drug, the gland is in a constant state of hypertrophy and hyperplasia. It is supposed that the block in the production of thyroxine occurs in the epithelial cells of the gland in spite of the fact that inorganic iodine is taken up by the gland. The conversion into organic iodine, however, does not occur, and this results in the formation of various partially iodinated thyronines and related analogues, as well as other compounds as yet unidentified. At present no one knows the harmful effects that such compounds may produce, but clinically, in addition to the persistence of a goiter or even a gradual increase in its size, there is continuous intoxication that has various side-effects. One of the most distressing is permanent paralysis of one or more of the extra-ocular muscles, particularly the superior rectus, resulting in vertical diplopia. Biopsies before and after an extended period of treatment with any of the so-called antithyroid drugs have shown that the gland never reverts to a normal histologic state. Some of the patients, in whom the enlargement of the thyroid gland has attained enormous proportions under the continuous use of these drugs, have been unable to assume a recumbent posture because of dyspnea. In some of these patients who were pregnant, the baby when born also had marked enlargement of the thyroid, a condition which may prove fatal to the infant. In such patients, despite operation and the administration of Lugol's solution for 3 weeks preoperatively, involution does not take place. The operations become very difficult because of the vascularity and friability of the gland, and therefore the danger of injury to the recurrent laryngeal nerves and the parathyroid glands is greatly increased.

Since 1920, when Neisser[1] reported that small quantities of iodine were well borne by patients with exophthalmic goiter and might bring about a marked improvement in their condition, many unrelated compounds have been used to bring about a euthyroid state and a permanent remission from the overactivity of the thyroid gland. To mention only a few there are, for example, thiourea, thiouracil, methyl, ethyl and propylthiouracil, carbimazole, and perhaps the most recent addition to this group has been potassium perchlorate. However, none of these so-called antithyroid drugs have proved entirely satisfactory, and some have been shown to be actually dangerous. The choice of the so-called "antithyroid drugs" to be used has depended largely on minor or severe side-effects encountered in their use. Shortly after its introduction thiouracil was found to have the greatest toxic propensities and produced agranulocytosis so frequently that it has no longer been sanctioned for clinical use. Toxic effects such as sore throat, elevation of temperature, agranulocytosis, leukopenia, and even purpuric reactions may develop following the use of any of the so-called antithyroid drugs. These complications may come on as rapidly as two days after the use of any of them, or on the other hand may develop slowly over a period of a few days, weeks, months, or years. Not infrequently deaths have been reported from agranulocytosis, following their use. A new drug, potassium perchlorate or sodium perchlorate, has been used frequently in Great Britain, Germany, and frequently in America. It is very effective in bringing about a euthyroid state, is inexpensive, and has been thought to have a low incidence of minor side-effects. Recently, however, following the use of this drug in the treatment of hyperthyroidism in a young, healthy woman at The Johns Hopkins Hospital, death occurred from aplastic anemia. Corticosteroid therapy and even splenectomy failed to improve the aplastic anemia which ended fatally two years after its onset.

Aplastic anemia was reported following treatment with carbimazole by Richardson and associates[2] in 1954 and Burrell[3] in 1956, with a fatal outcome in both patients. Aplastic anemia due to treatment with methimazole was reported by Levine and Rosenberg[4] in 1954. It would seem possible that aplastic anemia may occur especially in patients in whom the recognition of the toxic side-effects has been delayed and the drug used has not been promptly withdrawn.

In 818 recorded cases treated with potassium perchlorate an over-all incidence of 36 or 4% reactions were found. There have been other reports in the British literature. The case referred to in this editorial is believed to be the first in the American literature. Aplastic anemia occurs as a primary or idiopathic disease or secondary to exposure to a substance toxic to bone marrow. In the idiopathic form the aplasia is rarely a total one, some degree of cellularity of the bone marrow usually remains, in contrast to the nearly complete absence commonly found in the secondary types. In a recent number of the *British Medical Journal*, May 13, 1961, under "Medical Memoranda" there are two articles on "Aplastic Anaemia After Treatment of Thyrotoxicosis with Potassium Perchlorate,"—one by Quentin J. G. Hobson, West Middlesex Hospital, London,[5] and the other from Southend General Hospital by R. Sleigh Johnson and W. Z. Moore.[6]

It is impossible to know how many fatalities have occurred in this country from the use of the so-called antithyroid drugs, because such data are not available. It is therefore thought that in all but the most unusual or exceptional cases a combination of ablation therapy following only the necessary preoperative preparation is the safe method of therapy in the average case of hyperthyroidism. All of these drugs are in the experimental stage of development, and their actual pharmacologic action is ill understood. They are in reality probably antipituitary drugs for, after removal of the anterior lobe of the pituitary gland, they have no effect histologically on the thyroid gland. Their action when taken over a long period of time may be dangerous and can end fatally.

The course of patients to whom these drugs are being administered should be followed carefully and constantly by their physicians,

1. Neisser, E.: Ueber Jodbenhandlung bei Thyreotoxikose, Berl. Klin. Wchnschr. 17:461, 1920.
2. Richardson, J. S., Sarkany, I., and Campbell, C. D.: Fatal Case of Marrow Aplasia after Treatment with Carbimazole, Brit. M. J. 1:364, 1954.
3. Burrell, C. D.: Fatal Marrow Aplasia after Treatment with Carbimazole, Brit. M. J. 1:1456, 1956.
4. Levine, B., and Rosenberg, D. V.: Aplastic Anemia During the Treatment of Hyperthyroidism with Tapazole, Ann. Int. Med. 41:844, 1954.
5. Hobson, Q. J. G.: Aplastic Anaemia Due to Treatment with Potassium Perchlorate, Brit. M. J. 1:1368, 1961.
6. Johnson, R. S., and Moore, W. G.: Fatal Aplastic Anaemia after Treatment of Thyrotoxicosis with Potassium Perchlorate, Brit. M. J. 1:1369, 1961.

both from the clinical and the laboratory standpoint. Even after repeated verbal warnings concerning the side-effects of antithyroid agents, intelligent patients may fail to report for blood examinations until a serious blood dyscrasia produces severe manifestations of ill health. The early recognition of the toxic side-effects and the prompt withdrawal of the drug may contribute to the avoidance of serious clinical results or fatal toxic effects.

WILLIAM F. RIENHOFF, JR., M.D.

IDIOPATHIC NEUROPATHY AS A SIGN OF CANCER

In the past few years there has been an increasing recognition that the initial manifestation of a malignant lesion growing within the body may be idiopathic neuropathy. Holt,[1] who has recently reviewed this topic, calls attention first to the vascular basis for syndromes of multiple involvement of body systems. He points to diabetes mellitus, the Landry-Guillain-Barre syndrome and the polyneuropathies of the collagen diseases, and then concentrates upon neural symptoms as the first warning of cancer. (Such neuropathy is not related to mechanical effects of neoplastic growth such as infiltration, metastases or pressure, but seems related rather to the causes of cancer than its presence.)

The author speculates about the cause and pathogenesis of this lesion. Auto-immune responses to a malignant process may be a possibility, — an antigen-antibody reaction between a foreign protein and the small blood vessels of the nerves. Neuritis, neuralgia, or dysfunction of nerve tissue may occur as an inflammatory process, as well as from impedance to or alterations in its vascular supply. Such disturbances bring up for possible etiologic considerations viral infections. Certainly these infectious agents may be involved in neuritis and neuralgias. Invasion of dorsal ganglia by lymphomatous tissue has been accompanied by manifestations due to the herpes zoster virus. Holt calls attention to reports of varied apparent relationships between herpes zoster and malignancy, — neoplasia appearing in areas of former zoster involvement, cutaneous metastases in the herpetic lesions.

Actually of greater interest are the idiopathic and often multiple neuropathies accompanying the localized growth of cancer. Holt says that this has been reported with increasing frequency during the past half century. He emphasizes that it is essential to recognize "that the neural syndrome may have developed, resolved, or terminated fatally prior to the appearance of any clinical evidence of malignancy." It often appears as long as three years before the clinical manifestation of the neoplasm. (The implication is that the diagnostician look with care at the person having a neuropathy.) Neural disease has been associated with lymphoma, myeloma, reticulosis and carcinoma. Of the latter, frequent sites have been carcinoma of the lung (the most frequent), breast, gastrointestinal tract, ovary, uterus, rectum, lymph node and bone marrow.

The neuropathy may involve one neural tract which may persist, or may develop into a polyneuropathy; it not uncommonly has both sensory and motor manifestations. It may show itself as subacute combined degeneration, cerebellar atrophy, encephalopathy, and as Wernicke's or Korsakoff's disease.

The vascular lesions accompanying malignancy have shown interesting relationships. Thus, the pulmonary osteoarthropathy associated at times with pulmonary malignancy may have a basis in peripheral vascular lesions. The hyper-immune vasculitis of the collagen diseases and its relationship to neuropathy is well documented. Dermatomyositis and scleroderma have been associated with, and antedated the clinical manifestations of malignancy. (One review of well over 590 cases of dermatomyositis claims that 15 per cent were associated with neoplasia.) Myasthenias and myotonias also have been reported in association with malignancies.

With an aging population and the accompanying increasing incidence of malignancy, idiopathic neuropathy will have an increasing significance. The physician, after considering the more common causes of such lesions of the past—diabetes, poisoning by drugs and metals, and more recently the vasculitis of collagen diseases, will need to think too of hidden malignancy. He then will need to take whatever steps may be necessary to complete his search for such a lesion, not only at the moment but in coming months or years because of the not unusual lapse of time between the appearance of the neuropathy and the manifestations of the malignancy.

1. Holt, George W.: Idiopathic Neuropathy in Cancer. A First Sign in Multiple System Syndromes Associated with Malignancy, Am. J. M. Sc. 242:93, 1961.

A complete meeting

Welcome to Big "D"

for the 55th Annual Meeting of the Southern Medical Association

Dallas, Texas November 6-9, 1961

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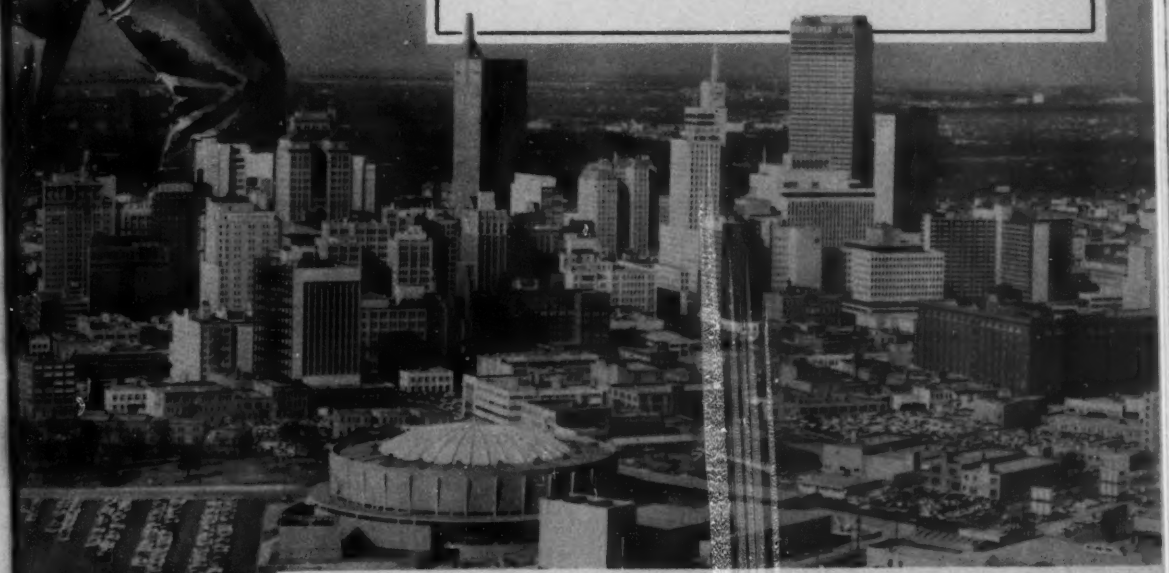

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55th Annual Meeting

DALLAS

November 6-9, 1961

SOUTHERN MEDICAL ASSOCIATION

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- Symposia on Medicoeconomics and other timely subjects
- 21 Scientific Sections

  Allergy
  Anesthesiology
  Dermatology & Syphilology
  Gastroenterology
  General Practice
  Gynecology
  Industrial Medicine & Surgery
  Medicine
  Neurology & Psychiatry
  Obstetrics
  Ophthalmology & Otolaryngology
  Orthopedic & Traumatic Surgery
  Pathology
  Pediatrics
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  Plastic & Reconstructive Surgery
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  Radiology
  Surgery
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- 21 Section Guest Speakers—outstanding men from each of the 21 Specialties from all sections of the country.
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- President's Night—Dinner-Dance—evening of gala entertainment
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25 YEARS AGO

Cerebral Lesions in Uncomplicated Fatal Diabetic Acidosis.*

"A Diabetic ought not to die from uncomplicated coma. . . .

"The clinical picture of these patients in the terminal stages is strikingly similar, the outstanding features being the very low blood pressure, the rapid heart rate and usually a sharp rise in temperature. These features may be present when the patient is admitted but more often appear after the coma treatment has been begun. Not infrequently they are present when good response is obtained to treatment as measured chemically by a rising plasma CO_2. Lande has reported similar findings and found that recovery was rare in the presence of both cardiovascular failure and marked hyperpyrexia. Several investigators have predicted a cerebral factor but to our knowledge no one has demonstrated a cerebral lesion or explained its physiologic modus operandi.

"We have studied 8 cases in which no adequate gross pathologic cause of death could be found; all were without demonstrable infection; the diabetes was of comparatively short duration; and the patients were young enough to minimize the usual degenerative vascular changes. . . .

"Postmortem examination of the various organs in summary showed varying amounts of myocardial degeneration, congestion and cloudy swelling of the other organs. Our interest, however, was chiefly in the brain, of which detailed studies were made. . . .

"*Description of Cerebral Lesions.* In cases of diabetic acidosis, the subarachnoid space is moderately widened, the veins show dilatation and stasis with escape of both serum and cellular contents. . . .

"In the cortex, the capillary bed is dilated and shows degenerative changes in the endothelial cells. The small cortical vessels show similar changes with, additionally, the increase of the adventitial cells. There is perivascular edema and often masses of blood pigment in the perivascular space.

"The cellular architecture is disturbed by the loss of ganglion cells, especially in foci in the third and fourth layers. The ganglion cells, themselves, show pericellular edema, with shrinkage of the cell. . . .

"In the choroid plexus, the vessels in the tufts show extreme stasis with degenerative changes in the walls, and collagen fibers filling the space between the vessels and the epithelial layer. . . .

"In the basal ganglia the vascular changes are more intense than in the cortex. Here the dilated perivascular spaces often contain collagen fibers, fibroblasts, and occasional macrophages filled with blood pigment. This is most marked in the large subependymal veins. The effects of this tissue edema vary greatly in the basal nuclei. . . .

"*Summary of Pathologic Brain Changes.* In brief, the brain in fatal diabetic acidosis shows lesions like those seen in acute asphyxia. The primary pathologic changes occur in the cerebral capillary bed. The capillaries are dilated, and the endothelial cells show degenerative changes with increased permeability of the walls as evidenced by the presence of perivascular and pericellular edema. . . .

". . . Because of its structural makeup, the choroid plexus is severely damaged.

"*Discussion.* At present, we have no exact knowledge of the mechanism of production of the cerebral anoxia in diabetic acidosis. . . . We feel that there is cerebral anoxia, primarily based upon reduced blood volume with hemo-concentration. As the result, there is marked reduction in blood pressure both systolic and diastolic. This causes a reduced cerebral blood flow since it has been shown that cerebral blood flow passively follows changes in blood pressure. . . .

"The increased permeability occasions cerebral edema. Once the edema is established rapid death of the cells takes place due to their intolerance of stagnant tissue fluids, and their high oxygen requirements. . . .

"We have postulated the possibility, that the cerebral lesions may be due to circulatory cerebral decompensation. It is our belief that when the cerebral lesions become irreversible, due to long continued cellular anoxia, they further embarrass cardiac function, by paralysis of the vasomotor and other vegetative centers, so that in spite of an improvement in the acid base balance, the patient dies from vasomotor collapse or from failure of respiratory or cardiac function."

*Dillon, E. S., Riggs, H. E., and Dyer, W. W.: Cerebral Lesions In Uncomplicated Fatal Diabetic Acidosis, Am. J. M. Sc. 192:360, 1936.

OVERLOOK SOMETHING?

Have you made your reservations for the 55th Annual Meeting of Southern Medical Association in Dallas, November 6-9, 1961? The hotel reservation form appears in this issue on page 1037.

Four Outstanding Symposia Featured on Dallas Program

Four Symposia will be featured as a part of the scientific program when Southern Medical Association holds its 55th Annual Meeting in Dallas, Texas, Nov. 6-9, 1961. These Symposia are in addition to the 52 half-day sessions scheduled by 21 scientific sections.

Three of the Symposia are "new" to SMA meetings—Immunologic Disorders and Transplantations, Cosmetic Problems in General Practice, and When Disaster Strikes! A fourth Symposium, on Medicoeconomics, is being featured again this year as it was such a successful and informative part of the St. Louis Meeting in 1960. This Symposium will be entirely new, delving into the various problems faced by the doctor in the nonmedical side of his profession.

The outstanding array of distinguished guest speakers from all parts of the country assures all physicians of an invaluable postgraduate program.

1. Symposium on Immunologic Disorders and Transplantations

This Symposium, to be presented Monday, November 6, at 8:30 a.m., will encompass many specialties of the medical field. The inter-related topics to be covered and the various specialties which each topic would include are: auto-immunity (medicine, surgery, and dermatology); the delayed hypersensitivity reaction (plastic and reconstructive surgery, ophthalmology, allergy, and orthopedic surgery); and clinical problems in immunity (anesthesiology, pediatrics, allergy, medicine, and surgery). Thus, this Symposium will offer points of interest to *all* physicians, regardless of primary interest.

Dr. Clifford C. Snyder, Miami, Florida, Chairman, will introduce the speakers. Dr. John J. Trentin, Houston, Texas, will discuss "Immunologic Tolerance—Fact or Fiction?" He will present the various experimental methods whereby animals can be rendered "immunologically tolerant" of skin and bone marrow homografts. Lymphoid chimerism data will be presented indicating that the mechanism of "classical" immunological tolerance is not what it was originally believed to be.

The next speaker will be Dr. Charles C. Sprague, New Orleans, Louisiana. His topic is "Auto-immunity in Clinical Medicine." He will review the basic work that has been done relative to applied immunology, relate it to clinical disorders thought to be explained by auto-immunity and postulate how this information may be used to facilitate homologous tissue transplantations.

Dr. Frederick G. Germuth, Jr., Charlotte, North Carolina, has the subject "Collagen Vascular Diseases." Under certain circumstances, experimental allergic reactions may be associated with marked vascular and renal alterations. What bearing do these experimentally induced lesions have upon their human counterparts?

Dr. Robert A. Nelson, Jr., Miami, Florida, will be the next speaker, his title to be announced.

"Immunological Aspects of Bone Transplantation" will be explored by Dr. William F. Ennicking, Gainesville, Florida. He will present a brief resumé of the fate of fresh autogenous and homogenous bone transplants. The histological fate of homogenous and heterogenous bone transplants under varying immunological settings including the second set phenomenon, parabiosis, total body irradiation, versene extraction, post-transplant immunization, and passive transfer will be presented and summarized.

Dr. Donald J. Blaney, Cincinnati, Ohio, will present "Serum Complement in Various Allergic Dermatoses." He will describe a study where hemolytic complement activity in groups of patients with various allergic disorders was compared to other disease states and to normal individuals. The most noteworthy variation from normal was a markedly decreased complement in active systemic lupus erythematosus.

Featured next on the program will be

Dr. Edgar T. Beddinfield, Jr., Stantonsburg, North Carolina, with the topic "Problems of Immunologic Disorders and Hypersensivity as Related to General Practice." He will summarize the potential role of the general practitioner in being well informed regarding the continuing progress in the field of tissue transplants so that he might be alert to the possibilities for benefit to his patients.

The subject "Clinical Experiences with Human Organ Transplants" has been chosen by Dr. Joseph E. Murray, Boston, Massachusetts.

Concluding this Symposium will be Dr. Blair Oakley Rogers, New York, New York, speaking on "The Implications of Variations in the Second and Third Set Homograft Responses in Genetically Related Individuals." Until recently, the classical "second set response" obtained in homografting was considered a routine phenomenon demonstrating a classical acquired immune reaction in the individual rejecting homografts of any tissue. Recent observations of skin homografts transplanted in first sets, second sets, and third sets, have demonstrated that the classical second set response has wide variations. The implications of these variations will be discussed in terms of their analogy to recent behavior of homografts of tissues and organs transplanted between closely related human volunteers and donors, and their hosts.

2. Symposium on Medicoeconomics

This program will be presented on Wednesday, November 8, at 2:00 p.m. It will be directed at the business and legal problems the doctor has in his office, especially as pertains to taxes. Practical pointers will be given on the preparation of income tax returns filed by physicians. The importance of proper business procedures and records in the doctor's office will be emphasized. Reasons for professional liability action against physicians are also to be given.

3. Symposium on Cosmetic Problems in General Practice

Presented in collaboration with the American Medical Association Committee on Cosmetics, this Symposium will be featured on Wednesday, November 8, at 2:00 p.m., with Dr. Stephen Rothman, Chicago, Illinois, as Chairman. The speakers and their topics include: Dr. Raymond R. Suskind, Cincinnati, Ohio, "Cutaneous Cleansing in Health and Disease"; Dr. Donald J. Birmingham, Cincinnati, Ohio, "Skin Protection in the Household and on the Job"; Dr. Albert M. Kligman, Philadelphia, Pennsylvania, "Care of the Hair and Nails"; and Dr. James W. Burks, New Orleans, Louisiana, "Dermatitis Due to Cosmetics." A discussion period will follow the presentations.

4. Symposium: When Disaster Strikes!

Dr. J. R. Maxfield, Jr., Dallas, Texas, is the Chairman of this Symposium which will be presented on Thursday, November 9, at 8:15 a.m. During his introductory remarks Dr. Maxfield will emphasize the importance of this topic. Disaster preparation is like having insurance. The importance of each individual to rally to the call for help in a disaster as well as his own personal preparation for any disaster will be stressed. The scientific consideration and research that industry is giving to survival through proper preparation of essentials such as foods, medications, and utility items will be presented by adequate exhibits and informative brochures.

"The Role of the Federal Government in Civil Defense and Disaster Relief" will then be discussed by a speaker to be named by the Honorable Frank Ellis, Director, Office of Civil Defense Mobilization, Washington, D. C. The speech will include the importance of the Office of Civil Defense Mobilization in a disaster along with the progress that has been made to date, the plans for the present, and a look into the future.

Col. Homer Garrison, Jr., Austin, Texas, Director of the Texas Department of Public Safety, will present "The Texas Blueprint for Survival." This blueprint is a working plan, realistic rather than theoretical because it has been tested time and again in various disasters of nature which create problems similar to those which might be expected in the event of a thermonuclear attack upon our homeland.

The concluding speaker will be Dr. Edward Teller, Berkeley, California. He has chosen the subject "The Importance of Preparation for Survival in a Thermonuclear Blast." He will stress the importance of preparation from the military as well as from the civilian standpoint. The need for complete civilian cooperation in order to support and achieve the military effectiveness for our country will be pointed out. Ways for survival will be suggested and discussed.

Radiology Refresher Courses: Postgraduate Instruction

As an experiment in postgraduate education, the Radiological Society of North America in cooperation with the Southern Medical Association will present four Refresher Courses during the annual meeting of the Southern Medical Association at the Adolphus Hotel in Dallas, Texas.

Attendance is limited to radiologists, including graduate students and residents in radiology, and medical students certified by the deans of their respective medical schools. Members of the Radiological Society of North America may attend the courses without charge. A registration fee of $10 will be charged to other radiologists with the exception of graduate students and residents in radiology, members of the Armed Forces on temporary duty, and medical students certified by the deans of their respective medical schools. All must register at the Registration Desk. Payment of the registration fee by non-members is *not* to accompany the request for tickets but is to be paid at the time of registration. All Refresher Course tickets will be held at the Registration Desk in the Adolphus Hotel. Please call for them there. Positive identification will be required for non-members and guests for admission to the Refresher Courses. If you cannot use the tickets you have reserved, please notify the Refresher Course Committee.

Admission to the Courses will be by presentation of the registration badge and a ticket for the desired Course. Read the description of the Courses, noting particularly the dates and time, and make your selection. Turn to the colored insert and indicate thereon those Courses which you wish to attend and mail the request promptly. The number attending the Courses will be limited by the capacity of the room, and requests for tickets will be honored in the order in which they are received. You will be notified regarding the availability of tickets as soon as possible after receiving your request.

We would appreciate suggestions concerning these Courses as they are presented, as well as your thoughts as to the desirability of this type of course at the Southern Medical Association. Please send any comments you may have to the Chairman of the Refresher Courses Committee: John D. Reeves, M.D., University of Florida Hospital, Gainesville, Florida.

Course No. 1: Tuesday, Nov. 7, 1:30-3:00 P.M.

Some Fundamentals of Chest Roentgenology

BENJAMIN FELSON, M.D., Cincinnati, Ohio

This course will deal primarily with principles rather than with specific disease entities. The material to be presented will be different from that of earlier refresher courses by the author. It will include the following:

1. The hila and pulmonary vasculature.
2. The pleura.
3. The diaphragm.

Course No. 2: Tuesday, Nov. 7, 3:30-5:00 P.M.

Recent Advances in Gastrointestinal Radiology

RICHARD H. MARSHAK, M.D., New York, New York

The course will be divided in four parts.

Part I:

Newer concepts in the interpretation of lesions of the gastrointestinal tract.

Part II:

Roentgen findings in the recently described syndromes such as the Zollinger-Ellison syndrome, Peutz-Jaeger's disease, carcinoid syndrome, toxic dilatation of the colon, villous adenoma, etc.

Part III:

Technical factors in the examination of the gastrointestinal tract as well as a discussion of the various barium preparations.

Part IV:

Questions and answers.

Course No. 3: Wednesday, Nov. 8, 1:30-3:00 P.M.

Recent Advances in Gastrointestinal Radiology

RICHARD H. MARSHAK, M.D., New York, New York

(Continued from Tuesday, Course No. 2)

Course No. 4: Wednesday, Nov. 8, 3:30-5:00 P.M.

Roentgenography of the Plain Skull

WILLIAM B. SEAMAN, M.D., New York, New York

A review of the fundamental principles of the interpretation of the skull roentgenogram with particular emphasis on the evaluation of the sella turcica and the differential diagnosis of intracranial calcifications. The problem of the differential diagnosis of cranial hyperostoses will be presented and the differentiation of fibrous dysplasia and the hyperostoses associated with meningiomata, discussed in detail.

REFRESHER COURSES

THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

at the

SOUTHERN MEDICAL ASSOCIATION MEETING

November 6 through 9, 1961

DALLAS, TEXAS

SEE INSTRUCTIONS ON REVERSE SIDE

(Detach Here)

FILL OUT THE FOLLOWING

(You must identify yourself at the Registration Desk)

(Print or type).....

Last Name First Name or Initials

.....

Street Address

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City State

CHECK THE FOLLOWING

Member R.S.N.A. ☐ Member S.M.A. ☐ Guest ☐

Resident or Fellow in Radiology at present ☐ Where .....

Medical Student* ☐ Where.....

Reserve Officer on Active Duty at present ☐

******You must present a letter of identification from the Dean of your Medical School.*

Fill out, also, the enrollment diagram on the reverse side of this page.

INSTRUCTIONS FOR ENROLLMENT

Read the accompanying description of the courses and plan of presentation. Register early; the number admitted to each course will be limited by the seating capacity of the room. Reservations will be made in the order of the receipt of request. Admission to the Refresher Courses will be by badge and tickets.

Courses will be limited to radiologists, including graduate students and residents in radiology, and medical students certified by the deans of their respective colleges.

All tickets will be held for you at the R.S.N.A.-S.M.A. Registration Desk at the Adolphus Hotel.

The registration fee, where applicable, will cover the cost of the Refresher Courses. Members of the Radiological Society of North America, guest speakers of the Section on Radiology of the Southern Medical Association, residents or fellows in radiology, medical students, and members of the Armed Forces on temporary duty do not pay a registration fee. Radiologists who are not members of the R.S.N.A. will pay, *at the time of registration,* a fee of $10.00.

If you cannot attend the course reserved for you, kindly notify the R.S.N.A.-S.M.A. Registration Desk. The seating capacity is very limited in some of the courses and your notice will allow another to attend.

Please Indicate (By Check-Mark) Which Sessions You Wish to Attend

Tickets Will Be Picked Up at Time of Registration

(Check Here)	*Course No.*	*Date and Time*	*Title and Instructor*
_____	1	Tuesday, Nov. 7 1:30-3:00 p.m.	Fundamentals of Chest Radiology—Felson
_____	2	Tuesday, Nov. 7 3:30-5:00 p.m.	Recent Advances in Gastrointestinal Radiology (Part I)—Marshak
_____	3	Wednesday, Nov. 8 1:30-3:00 p.m.	Recent Advances in Gastrointestinal Radiology (Part II)—Marshak
_____	4	Wednesday, Nov. 8 3:30-5:00 p.m.	Radiology of the Plain Skull—Seaman

Mail this order sheet to William H. Neil, M.D., R.S.N.A.-S.M.A. Refresher Course Committee, 1217 West Cannon Street, Fort Worth 4, Texas, prior to November 1. After November 1, c/o Southern Medical Association, R.S.N.A. Refresher Courses, Adolphus Hotel, Dallas, Texas.

DO NOT SEND MONEY WITH THIS APPLICATION

SOUTHERN MEDICAL NEWS

State News Items

The Fourth Annual Medical Progress Assembly will be held in Birmingham, Alabama, Sept. 17-19, 1961, at the Dinkler-Tutwiler Hotel. Presented by the Birmingham Academy of Medicine, the Assembly will feature 17 authorities who will lecture on subjects ranging from allergy to urology. The Assembly has been accepted for 14 hours of Category I credit by the American Academy of General Practice. Special entertainment events have been planned for both physicians and their wives. For further information write: Birmingham Academy of Medicine, Medical Progress Assembly, P. O. Box 2591, Birmingham, Alabama.

The American Urological Association offers annual awards totaling $1,000.00 for essays on the result of some clinical or laboratory research in urology. The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Bellevue-Stratford Hotel, Philadelphia, Pennsylvania, May 14-17, 1962. For full particulars write the Executive Secretary, William P. Didusch, 1120 North Charles Street, Baltimore 1, Maryland. Essays must be in his hands before Nov. 15, 1961.

The next scheduled examination of the American Board of Obstetrics and Gynecology (Part 1), written, will be held on Jan. 5, 1962. Current bulletins listing requirements for examination may be obtained by writing to Dr. Robert L. Faulkner, Executive Secretary and Treasurer, 2105 Adelbert Road, Cleveland 6, Ohio.

ALABAMA

Dr. Chester W. White, Jr., has been appointed Chairman of the University of Alabama Medical Center's Department of Anesthesiology. Dr. White will replace Dr. Alice McNeal, who will continue in the Department as Professor.

Officers elected by the Alabama Radiological Society are: Dr. Samuel F. Crabtree, Anniston, President; Dr. Richard D. Glasgow, Fairfield, Vice-President; and Dr. Walter J. Brower, Birmingham, Secretary-Treasurer.

ARKANSAS

Dr. Fount Richardson, Fayetteville, head physician at the University Infirmary and Past President of the American Academy of General Practice, was awarded the highest award the University of Arkansas and its Alumni Association can bestow upon an alumnus at the recent Spring Commencement Ceremony. Dr. Richardson is First Vice-President of Southern Medical Association.

Dr. Winston K. Shorey, former Associate Dean of the University of Miami School of Medicine, has become Dean of the School of Medicine at the University of Arkansas in Little Rock.

Several county medical societies in Arkansas have announced new members: *Ashley,* Dr. James A. Sims, Wilmot; *Baxter,* Dr. John F. Guenthner, Mountain Home; *Craighead-Poinsett,* Dr. Joseph H. Poff, Trumann; and *Jefferson,* Drs. Clement D. Burroughs and William Joe James, both of Pine Bluff.

FLORIDA

Dr. John A. D. Cooper will be installed as Dean of the University of Miami School of Medicine some time this Fall, it has been announced by Dr. Jay F. W. Pearson, President of the University. Dr. Cooper is at present Associate Dean of Northwestern University Medical School and also Professor of Biochemistry.

Dr. George N. Papanicolaou has been named Director of the Cancer Institute in Miami. He will assume his post in October, ending 48 years of association with Cornell University Medical College, where he is Professor Emeritus of Clinical Anatomy.

Dr. John S. Stewart, Fort Myers, has joined Dr. Floyd K. Hurt, Jacksonville, on the Board of Directors of the Florida Medical Service (Blue Shield). Dr. Hurt is also Treasurer of the corporation.

Dr. Homer L. Pearson, Jr., Miami, has been named to the Board of Trustees of the American Medical Association.

Dr. Norman F. Coulter, Orlando, is the new President of the Orange County Medical Society.

MARYLAND

Dr. Charles F. O'Donnell, Towson, is the new President of the Medical and Chirurgical Faculty of the State of Maryland.

Dr. John C. Hume has been appointed Professor of Public Health Administration at Johns Hopkins University School of Hygiene and Public Health in Baltimore.

Dr. Ruth Auguste Vankai, Silver Spring, has been elected to Fellowship in the American College of Anesthesiologists.

MISSISSIPPI

Dr. Fred Allison, Jackson, is President of the newly-named Mississippi Thoracic Society, formerly the Mississippi Trudeau Society. Other officers are Dr. John F. Busey, Jackson, Vice-President; and Dr. Jack Herring, Sanatorium, and Dr. Blair Batson, Jackson, both members of the Executive Council.

Dr. Clyde Watkins, Sanatorium, Superintendent of the Mississippi State Sanatorium, is President of the Mississippi Tuberculosis Association.

Recently certified by the American Board of Obstetrics and Gynecology were the following Mississippi physicians: Dr. John N. Harrington, Columbus; and Dr. John E. Lindley, Meridian.

Dr. Watts R. Webb, Jackson, has been elected a Councilor of the American Thoracic Society.

Officers of the Mississippi EENT Association are Dr. Donald S. Hall, Vicksburg, President; Dr. Joseph B.

Continued on page 62

Awards of the Southern Medical Association

Do you know of a deserving member of Southern Medical Association whom you would like to nominate for one of the following Awards? If so, you are requested to complete the required forms for nomination at your earliest convenience. These awards will be presented to the recipients at the Fifty-Fifth Annual Meeting in Dallas, November 6-9, 1961.

DISTINGUISHED SERVICE AWARD

"The Distinguished Service Award of the Association may be awarded annually to any member of the Association in recognition of outstanding contributions to the advancement of medical science. Any member of the Association shall be eligible to receive the award and nominations may be made by any member of the Association."

This award was established in 1955 and has been bestowed upon five outstanding Association members.

RESEARCH MEDAL

"The Research Medal may be awarded from time to time to a member of the Association for meritorious and original research work provided the member has made contributions of sufficient importance to merit this distinction; the Council to provide for a proper committee to evaluate research work and report to the Council."

This award was established in 1912 and has been awarded a total of seventeen times, the last award being made at the St. Louis meeting in 1960.

SEALE HARRIS MEDAL

"The Seale Harris Medal may be awarded to some member of the Association as recognition for important research accomplishment in the broad field of metabolism, endocrinology, nutrition, or for research which contributes to a better understanding of the chemical changes occurring in disease."

This award, established at the New Orleans meeting in 1958, was awarded for the first time at the Atlanta meeting in 1959, and again at the St. Louis meeting in 1960.

METHOD OF SELECTION OF RECIPIENT

- Any member of the Association in good standing is eligible for nomination as a recipient of awards.

- Any member in good standing of the Association may nominate a recipient for awards.
- The nominations for the recipient are evaluated by an unpublicized committee which selects three of the nominees annually and submits their names to the Council of the Southern Medical Association.
- The Council elects annually one of the three submitted by the Committee on Special Awards as the recipient.
- The election by the Council is held during the Annual Meeting of the Association and the winner is publicly presented to the Association during the last general session of the membership at a given annual meeting.

MECHANICS

Certain rules and regulations governing mechanics for nomination for awards are provided in the Constitution. Any member of the Association desiring to place a fellow physician member in nomination may secure official forms upon which nominations shall be made from the headquarters office. Forms provide for:

- Biographical information on the nominee, including a recent photograph
- Medical education and training of the nominee
- A professional history, including private practice, specialty training, contributions to medical literature, teaching affiliations, staff connections, etc.
- A detailed description of a specific or general contribution or accomplishment of the nominee to the advancement of medical science or any of its phases upon which the nomination is to be based
- Substantiating evidence of merit, including printed materials, publications, articles, other citations, etc.

The completed forms (and no nomination can be processed without the completion of all proper forms) may be mailed to the Executive Secretary of the Association, 2601 Highland Avenue, Birmingham 5, Alabama, or mailed direct to the First Vice-President. The Committee on Special Awards will submit the names of not more than three nominees for each award to the Council during its first session at a given annual meeting and the election of the recipient by the Council shall be held at its first session.

The elected recipients will be notified of their election and shall receive the award at the last general session of the Association.

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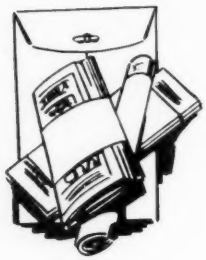

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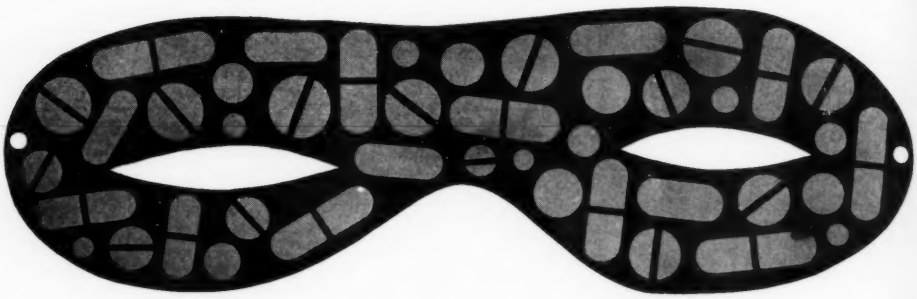

drugs anonymous

One of the several hastily conceived and potentially dangerous suggestions for reducing drug costs is generic-name prescribing. The proponents of generic-name prescribing claim that it will lower drug costs significantly and—through supervision by the Federal Government—provide quality equivalent to that of trademarked drugs. We maintain that these claims are false. Here are some authoritative answers to the principal questions posed by generic-name prescribing.

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Rhode Island Medical Journal,
January, 1961

Are the savings worth the risk of sacrificing quality?

". . . it is unsafe [to prescribe generically] because there is not sufficient policing of our standards. . . ."

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"The naive belief that, if a product was not good, the FDA would prohibit its sale is just not realistic. . . . it is completely impossible for the FDA to check every batch of every product of every manufacturer. . . . Hence the integrity and reputation of the manufacturer assume unusual significance where drugs and health products are concerned."

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In a study of 40 patients with bronchial asthma, 24 persons (60%) reported BRONKOTABS brought good relief from asthmatic symptoms – ease of expectoration, reduction of bronchospasm and increased vital capacity. Only seven patients failed to respond at all. "The combination of drugs used [in Bronkotabs] gave greater relief in these patients than the conventionally used tablet [ephedrine, theophylline, phenobarbital] . . ."[1]

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References: 1. Spielman, A. D.: Evaluation of a Combination Tablet of Theophylline, Ephedrine Sulphate, Phenobarbital, Thenyldiamine and Glyceryl Guaiacolate in the Treatment of Chronic Asthma, Ann. Allergy 18:281, 1960. 2. Waldbott, G.: Bronkotabs – a New Antiasthmatic Preparation (Preliminary Report), Int. Arch. Allergy 17:116, 1960.

For full information on Breon's five antiasthmatics, see pp. 538-539 of the 1961 PHYSICIANS' DESK REFERENCE plus the 2nd, 3rd, or 4th quarterly supplement.

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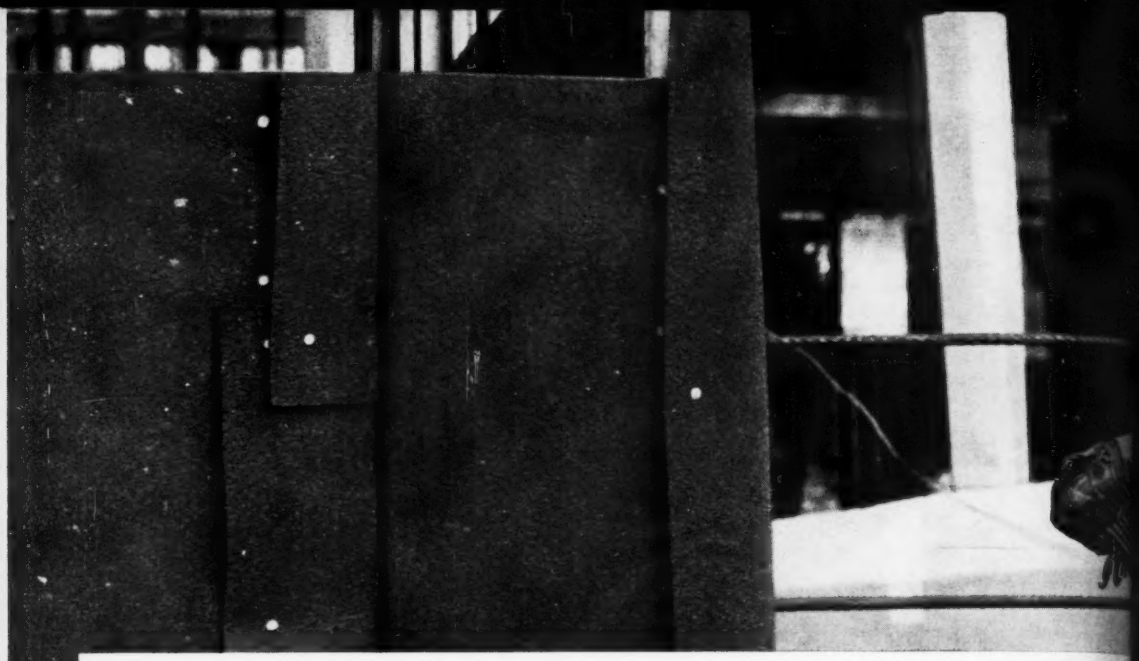

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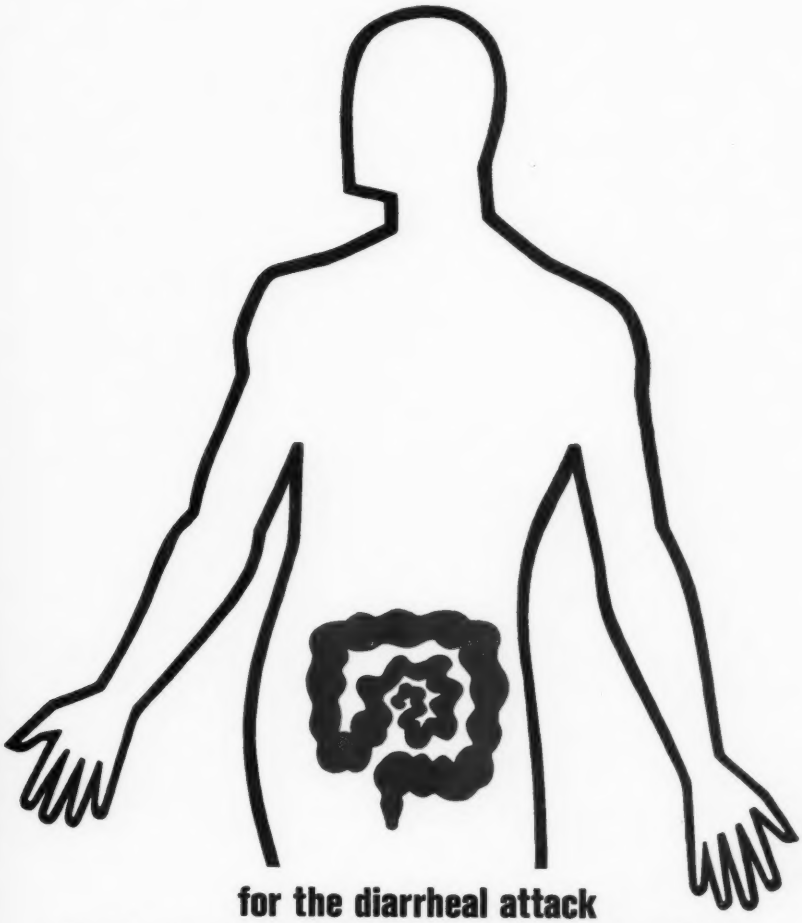

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FUROXONE LIQUID is a pleasant orange-mint flavored suspension containing FUROXONE 50 mg. per 15 cc., with kaolin and pectin.

1. Mintz, A. A.: Antibiot. Med. 7:481, 1960.

EATON LABORATORIES, Division of The Norwich Pharmacal Company, NORWICH, N. Y.

CAULDRON BUBBLE GASTRIC TROUBLE

Give immediate relief from heartburn and gastric distress with Al-Caroid. The fine-particle dispersion of balanced antacids in Al-Caroid quickly neutralizes excess gastric acid. The enzyme Caroid added to the Al-Caroid formula prevents interruption of protein digestion. When antacids raise the pH of stomach contents pepsin is inactivated, but the enzyme Caroid continues protein digestion in alkaline or acid media.

AL-CAROID®
antacid powder or tablets

American Ferment Division • Breon Laboratories Inc., New York 18, New York

Where's the arthritic this morning?

Thanks to Medrol Medules, he woke up comfortable and he's already on the go.

The first long-acting oral steroid, Medrol Medules gives the arthritic patient therapeutic action that continues through the night. In many cases, morning stiffness can become a thing of the past.

The slow, steady release of methylprednisolone often provides greater effectiveness, with less frequent administration and sometimes a reduced total daily dosage.

Many of your arthritic patients, too, can wake up comfortable on Medrol Medules.

Dosage: The following dosages are recommended in rheumatoid arthritis:

	Initial	*Maintenance*
Severe	12 to 16 mg.	6 to 12 mg.
Moderately severe	8 to 10 mg.	4 to 8 mg.
Moderate	6 to 8 mg.	2 to 6 mg.
Children	6 to 10 mg.	2 to 8 mg.

With Medrol Medules, it may be possible to reduce the total daily dose by ½.

Indications and effects: Medrol benefits (anti-inflammatory, antiallergic, antirheumatic, antileukemic, antihemolytic) have been demonstrated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

Precautions and contraindications: Because of Medrol's high therapeutic ratio, patients usually experience dramatic relief without developing such possible steroid side effects as gastrointestinal intolerance, weight gain or weight loss, edema, hypertension, acne, or emotional imbalance.

As in all corticotherapy, however, there are certain cautions to be observed. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, or active tuberculosis necessitates careful control in the use of steroids. Like all corticosteroids, Medrol is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia, or varicella.

Approximately 135 tiny "doses" mean smoother steroid therapy

Each capsule contains:
Medrol (methylprednisolone) 4 mg.
Supplied in bottles of 30 and 100.

Medrol* Medules*

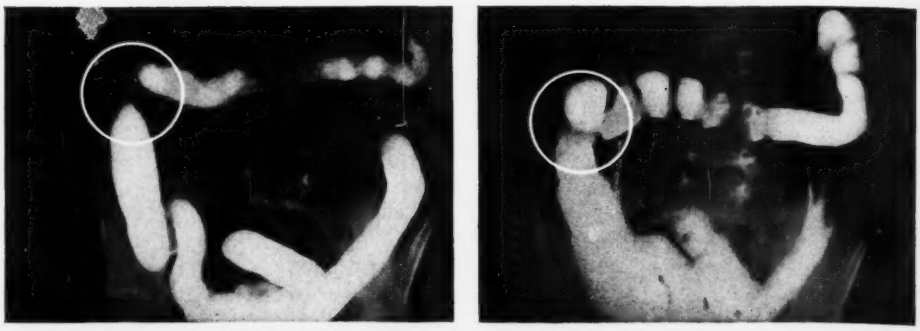
Upjohn

*TRADEMARK, REG. U.S. PAT. OFF. COPYRIGHT 1961, THE UPJOHN COMPANY JUNE, 1961 THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

ULCERATIVE COLITIS

5

Ulcerative Colitis is a difficult and distressing disease to treat. However, the outlook for the patient with chronic ulcerative colitis has been greatly improved since the introduction of the newer sulfonamides, such as Azulfidine, steroids, and antibiotics.



Hightower, N. C. and others. Amer. J. digest. Dis. 3: 861 (Nov) 1958

DIAGNOSIS ● Important clinical symptoms include recurrent bloody diarrhea, rectal tenseness, abdominal cramps, anorexia, weight loss, dehydration and occasional fever. Hemoglobin is often below normal, and E.S.R. elevated. Alterations of the rectal mucosa may be apparent upon examination.
Early diagnosis increases the possibility of successful medical treatment. Proctosigmoidoscopy and roentgen examination are essential for making a definite diagnosis.

TREATMENT ● Azulfidine® Brand of Salicylazosulfapyridine

Azulfidine is the most widely accepted sulfonamide for the treatment of ulcerative colitis. Administration of Azulfidine produces rapid regression of the ulcerative and inflammatory lesions of the bowel. Remission or considerable improvement has occurred in 70 to 80 per cent of the patients treated. Azulfidine is safe for long term administration because its toxicity is extremely low and drug reactions are rare.

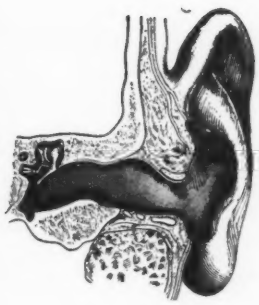
Film available on "The Early Detection and Medical Management of Chronic Ulcerative Colitis". 16 mm in sound and color, running 31 minutes. Address requests to Ideal Pictures Inc., 58 E. South Water Street, Chicago, Illinois.

Pharmacia Laboratories, Inc.

501 FIFTH AVENUE, NEW YORK, 17, N.Y.

three therapies of choice for infected /inflamed /painful ears

Rarely Sensitizing



1 'AEROSPORIN'® brand Otic Solution

Comprehensive bactericidal/antifungal action—eradicates *Pseudomonas* and most other common causes of otitis. Hygroscopic; restores normal acid mantle.

Each cc. contains:
'Aerosporin' brand Polymyxin B Sulfate ..... 10,000 Units
Acetic acid 1%
Propylene Glycol q.s. Sterile
Available in dropper bottles of 10 cc.

2 'CORTISPORIN'® brand Otic Drops

Broad-spectrum bactericidal action plus effective anti-inflammatory and antipruritic therapy. Eradicates most common causes of otitis; restores normal acid mantle.

Each cc. contains:
'Aerosporin' brand Polymyxin B Sulfate ..... 10,000 Units
Neomycin Sulfate ..... 5 mg.
Hydrocortisone in a sterile, slightly acid, aqueous suspension ..... 10 mg.
Available in dropper bottles of 5 cc.

3 'LIDOSPORIN'® brand Otic Solution

Acts quickly to relieve pain and itching associated with otitis externa. Bactericidal/antifungal action—eradicates *Pseudomonas* and most other common causes of otitis. Hygroscopic; restores normal acid mantle.

Each cc. contains:
'Aerosporin' brand Polymyxin B Sulfate ..... 10,000 Units
Xylocaine* HCl brand lidocaine Hydrochloride (5%) 50 mg.
Propylene Glycol q.s. Sterile
Available in dropper bottles of 10 cc.

*Reg. T.M. Astra Pharmaceutical Products, Inc. — U. S. Pat. No. 2,441,498

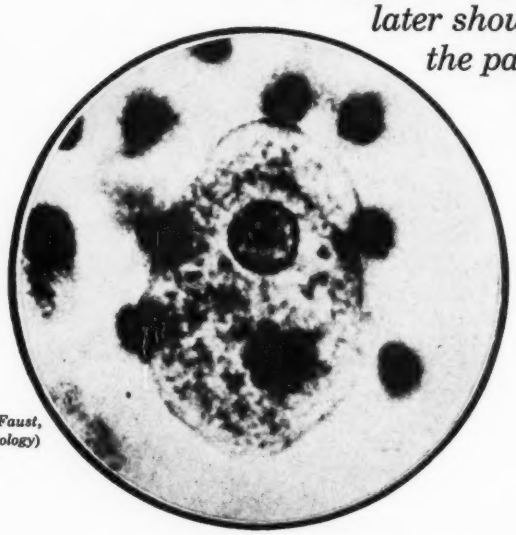
Literature available on request.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N. Y.

important new drug in the treatment of Amebiasis

90% cures with ANAMEBA®

Re-examinations four months later showed 90% of the patients were still cured.



(From Craig and Faust, Clinical Parasitology)

19% INCIDENCE: ANAMEBA SPECIFIC FOR AMEBIASIS

Frye and Lampert[1] recently studied the effect of Anameba in the treatment of asymptomatic Endameba histolytica carriers. They concluded that "Results of treatment . . . with Anameba in a group of 23 carriers of E. histolytica were excellent. No toxic reactions or side effects were noted among the 49 subjects who received the drug . . . There was no nausea, diarrhea or other sign of toxicity or side effects."

RESULTS OF POST-TREATMENT STOOL EXAMINATIONS FOR E. HISTOLYTICA

No. of Patients Examined	No. of Controls	No. Positive Before Treatment	No. Positive After First Course of Treatment
135	26	23	2

8 DAYS OF TREATMENT RESULTS IN 90% CURES

A single course of treatment (1 tablet t.i.d. for 8 days) results in improvement or complete alleviation of symptoms. Relief of symptoms of abdominal distress and flatulence is prompt. No toxic reactions or side effects occur, and no alteration in diet is necessary during Anameba therapy.

Each Anameba tablet contains: Iodochlorhydroxyquin 125 mg., and Bacitracin-methylene disalicylate 5000 U.S.P. Units. *Supplied:* In bottles of 24 tablets.

When you suspect amebiasis—specify ANAMEBA. For additional information, please write our Medical Department.

1. Frye, W.W., and Lampert, R.: Treatment of Asymptomatic Endamoeba histolytica Carriers with a Formulation of Bacitracin-Methylene Disalicylate and Iodochlorhydroxyquin (Anameba). (To be published in Am. J. Gastroenterol., October, 1960.)

CHICAGO PHARMACAL COMPANY
5547 N. Ravenswood Ave., Chicago 40, Ill.

In summer respiratory allergies,

the treatment problem is to relieve congestion. Valuable as antihistamines are against sneezing, itchy, weeping eyes and rhinorrhea, they are less effective against nasal congestion.[1]

NOVAHISTINE® DECONGESTS

Novahistine provides more than simple antihistaminic effect. It shrinks congested mucous membranes (nasal, pharyngeal, laryngeal, conjunctival), opens up air passages, promotes sinus drainage, and helps prevent mouth breathing.

NOVAHISTINE LP TABLETS

8 to 12 hour relief with a single adult dose of 2 tablets. Each tablet contains 25 mg. phenylephrine HCl (a vasoconstrictor that does not increase pulse rate) and 4 mg. chlorprophenpyridamine maleate (a potent, well-tolerated antihistamine).

NOVAHISTINE ELIXIR

exceptionally palatable liquid that children like to take. Each 5 ml. teaspoonful contains 5 mg. phenylephrine HCl and 2 mg. chlorprophenpyridamine maleate.

1. Beckman, H.: *Pharmacology: The Nature, Action and Use of Drugs*, 2nd Ed. W. B. Saunders Company, Philadelphia and London, 1961, p. 673.

PM

PITMAN-MOORE COMPANY
Division of The Dow Chemical Company
Indianapolis 6, Indiana

is pharmaceutical advertising really "advertising"?

of course it is, though some have called it "education" . . . not <u>really</u> "advertising."

Of course it's "advertising"... a frankly competitive activity of the American private enterprise system to which this industry belongs. Of course it's "advertising"...created in the hope of getting the physician to note and read; of persuading him, by setting forth proven indications and advantages, to learn about a drug; and of thereby helping him alleviate suffering or cure disease by prescribing it.

"Advertising"? Surely! BUT indisputably different from any other advertising in the world (which is just what has led people to devise various different names for it). For in its proper role it communicates the vital information . . . good, bad, and indifferent . . . and it keeps the physician abreast of each useful new clinical application and each new danger revealed during increasing use of the drug.

There's been a lot of talk about "over-advertising", and there may have been occasional excesses. But consider the potential dangers, in this era of astonishing new drugs, of "under-advertising". . . in view of the complexity of modern drug therapy; the lag of 6 to more than 18 months before the appearance of definitive medical articles on new drugs; and the fact that there is no other source of such comprehensive information about a new agent as the company that ran it through the crucial gauntlet of animal pharmacology and clinical investigation.

This message is brought to you on behalf of the producers of prescription drugs. For additional information, please write Pharmaceutical Manufacturers Association, 1411 K Street, N.W., Washington 5, D.C.

JUST AS A REMINDER...
6
E N T
products to remember!
AURALGAN®
IN ACUTE OTITIS MEDIA
SAFE AURALGESIC
AND DECONGESTANT
OTOS-MOSAN®
BROAD-SPECTRUM
THERAPY IN
SUPPURATIVE OTITIS
Now!
BIO-TOSMOSAN® HC
IN ACUTE EXACERBATION
EXTERNAL OTITIS
ALLERGIC EARS
RHINALGAN®
SAFE!
"NOT JUST ANOTHER
DECONGESTANT"
Now!
RHINALGAN® HC
ANTI-INFLAMMATORY
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LARYLGAN®
FOR INFECTIOUS
AND NON-INFECTIOUS
THROAT INVOLVEMENTS
DOHO CHEMICAL CORP. 100 VARICK ST. NEW YORK 13, N.Y.

vertigo is reversible

Antivert® stops vertigo

moderate to complete relief of symptoms in 9 out of 10 patients[1]

Prescribe one ANTIVERT tablet (or 1-2 teaspoonfuls ANTIVERT syrup) 3 times daily, before each meal, for prompt relief of vertigo, Meniere's syndrome and allied disorders. Side effects are short-lived, usually only harmless flushing and tingling associated with vasodilation. As with all vasodilators, ANTIVERT is contraindicated in severe hypotension and hemorrhage.

Supplied: Small blue-and-white scored tablets (meclizine HCl 12.5 mg. and nicotinic acid 50 mg.) in bottles of 100. Syrup (each 5 cc. teaspoonful contains meclizine HCl 6.25 mg. and nicotinic acid 25 mg.) in pint bottles. Prescription only. Bibliography available on request.

Reference: 1. Scal, J. C.: Eye Ear Nose & Throat Month. **38**:738 (Sept.) 1959.

And for your aging patients—
NEOBON® Capsules
five-factor geriatric supplement

Rx Roerig

New York 17, N.Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being®

Clinically Proven

in more than 750 published clinical studies
and over six years of clinical use

Outstandingly Safe and Effective

for the tense and
nervous patient

1 simple dosage schedule relieves anxiety dependably — without the unknown dangers of "new and different" drugs

2 does not produce ataxia, stimulate the appetite or alter sexual function

3 no cumulative effects in long-term therapy

4 does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis

5 does not muddle the mind or affect normal behavior

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; bottles of 50. Also as MEPROTABS*—400 mg. *unmarked*, coated tablets; and in *sustained-release* capsules as MEPROSPAN®-400 and MEPROSPAN®-200 (containing respectively 400 mg. and 200 mg. meprobamate).
*TRADE-MARK

Miltown®

meprobamate (Wallace)

WALLACE LABORATORIES / *Cranbury, N. J.*

CM-4728

MEDICAL NEWS

Continued from page 1045

Rogers, Oxford, President-Elect; and Dr. Samuel B. Johnson, Jackson, Secretary.

MISSOURI

Dr. Leonard T. Furlow, St. Louis, is President of the Harvey Cushing Society.

Dr. Albert B. Eisenstein, St. Louis, has been elected to membership in the American Society for Clinical Investigation.

Dr. David M. Skilling, Jr., St. Louis, has been elected Medical Director of the Tuberculosis and Health Society of St. Louis.

The University of Missouri Medical Center has several news items. Dr. Jack M. Martt, Associate Professor of Medicine, is a newly-elected faculty member of the University's Gamma Chapter of Alpha Omega Alpha, national honorary medical fraternity. Dr. George J. Lytton, Clinical Associate Professor of Psychiatry, has been elected a Fellow of the American Psychiatric Association. Six new appointments to the faculty have been announced: Dr. David R. Ginder, Associate Professor of Medicine; Dr. George W. N. Eggers, Associate Professor of Surgery (Anesthesiology); Dr. Fernando Tapia, Clinical Assistant Professor of Psychiatry; Dr. Ernest E. McCoy, Assistant Professor of Pediatrics; Dr. James F. Davenport, Jr., Assistant Professor of Pathology; and Dr. William H. Soderstrom, Assistant Professor of Medicine.

New members of various medical societies in Missouri include: *Butler-Ripley-Wayne County*, Dr. Orval E. Riggs, Poplar Bluff; *Jackson County*, Drs. Charles C. Gullett and George P. Williams, both of Kansas City; Dr. Herman J. Hausheer, Independence; and Dr. William R. Morris, Raytown; *Johnson County*, Dr. A. L. Falkner, Warrensburg; *St. Louis*, Drs. John T. Dolan, Jr., Robert F. Meger, Edwin C. Neville, and Herbert Sunshine, all of St. Louis; and *St. Louis County*, Drs. Daniel Roth and Sidney Saltzstein, both of St. Louis.

Dr. Cecil G. Leitch, Kansas City, is General Practitioner of the Year, as named by the Kansas City Chapter of the American Academy of General Practice.

Officers of the Missouri Heart Association include: Dr. William J. Shaw, Fayette, President-Elect; Dr. Guy Callaway, Jr., Springfield, Vice-President; and Dr. James A. Kinder, Cape Girardeau, Secretary.

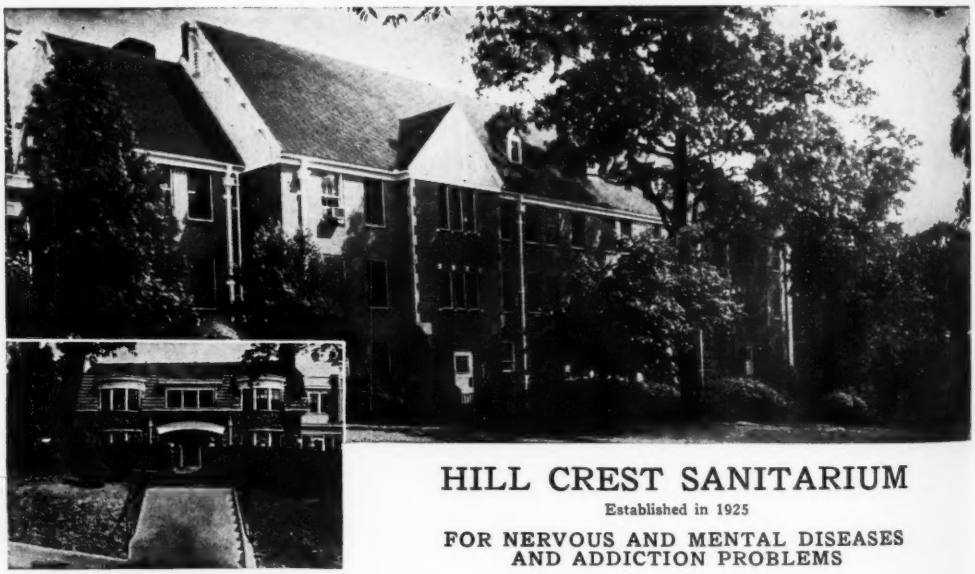
Officers of the North Kansas City Memorial Hospital include the following North Kansas City physicians: Dr. Robert H. Parker, President; Dr. G. Comer Bates, President-Elect; Dr. Truman B. Schertz, Vice-President; and Dr. Samuel L. Allen, Secretary.

Dr. James H. O'Neil is President of the Kansas City Surgical Society. Other officers are Dr. Paul R. Carpenter, Vice-President; and Dr. Hector W. Benoit, Secretary-Treasurer. The physicians are all of Kansas City.

Dr. G. Wilse Robinson, Jr., Kansas City, has been elected Speaker of the House of Delegates-Elect of the American Psychiatric Association.

The following Kansas City physicians are officers of the Kansas City Heart Association: Dr. M. Donald McFarland, President; Dr. Martin J. Mueller, President-Elect; and Dr. Philip G. Kaul, a Vice-President.

Continued on page 64



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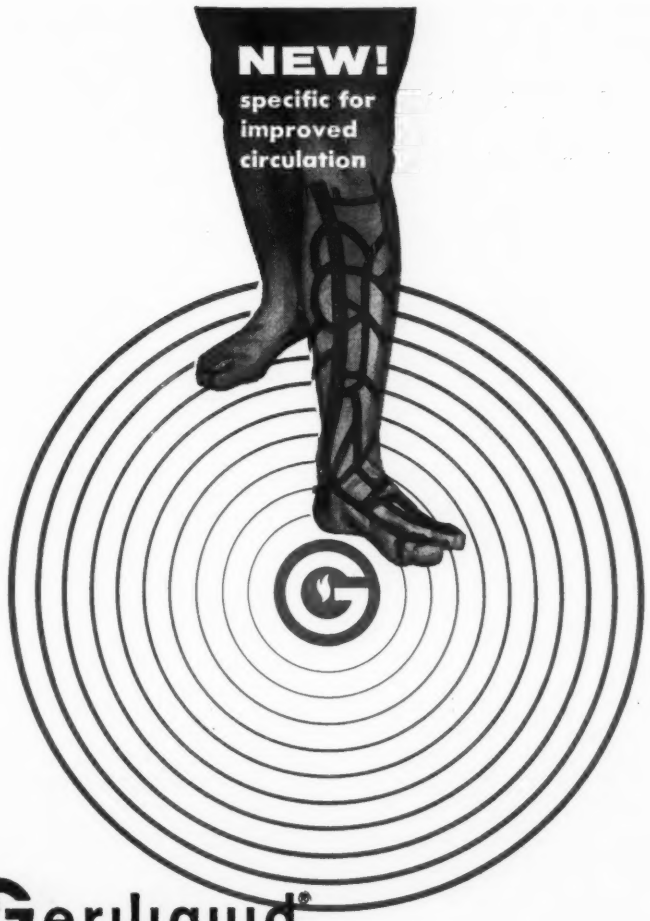
HILL CREST SANITARIUM

Established in 1925

FOR NERVOUS AND MENTAL DISEASES AND ADDICTION PROBLEMS

James A. Becton, M.D. James Keen Ward, M.D.

P. O. Box 2896, Woodlawn Station, Birmingham 6, Ala. Phone WO 1-1151 and WO 1-1152



Geriliquid®

NIACIN AND GLYCINE

PROVIDES SUSTAINED WARMTH OF EXTREMITIES

In patients with impaired peripheral circulation, Geriliquid warms cold hands and feet through rapid, safe vasodilation by niacin, and provides continuing sustained vasodilation and heat radiation by the thermogenic action of glycine.

Other Benefits:

- **Increases ability to walk farther with less pain**
- **Relieves pain, dizziness and faintness**
- **Improves appetite and brightens the mood**

Composition: Each 5 ml. contains: Niacin 75 mg., Glycine 750 mg. in a sherry wine base. Contains Alcohol 5%.

Dosage: One or two teaspoons three times daily before meals.

Supplied: 8 oz. bottles.

72240

LAKESIDE LABORATORIES, INC.
Milwaukee 1, Wisconsin

Continued from page 62

Two faculty members of the University of Missouri Medical Center have been elected Fellows of the American College of Physicians. They are Dr. Jack M. Martt, Associate Professor of Medicine, and Dr. Roland P. Landenson, Clinical Associate Professor of Medicine.

Three St. Louis physicians have been named officers of the recently chartered Missouri State Medical Foundation, a nonprofit corporation sponsored by the Missouri State Medical Association to aid medical students of Missouri. The officers are Dr. Raymond O. Muether, President; Dr. Leonard T. Furlow, Vice-President; and Dr. Charles A. Doyle, Secretary-Treasurer.

Dr. Samuel U. Rogers, Kansas City, has been elected the new President of the Florence Home.

Dr. Axel N. Arneson, St. Louis, has been re-elected Treasurer of the American College of Obstetricians and Gynecologists.

NORTH CAROLINA

New members of the Medical Society of the State of Carolina include: Dr. James B. Rymer, Charlotte; Dr. Wesley S. Garland, Marshville; Drs. John C. Doerr, Thomas E. Castelloe, Ausley Lee Denton, Jr., Thomas B. Greer, and Francis E. Winslow, Jr., all of Raleigh; Dr. Donald V. Chamblee, Broadway; Dr. Shelton Miller, Jr., Winston-Salem; Dr. James W. Wideman, Whiteville; Dr. Stephen C. Pugh, Chadbourn; Dr. Hewlett C. Connell, Wendell; Dr. Alexander C. McLeod, New York, New York; Dr. John P. Holt, Asheville; Dr. Sarah A. Morrow, High Point; Drs. Henry Abernethy, Charles Trado, and Lee Seagle, all of Hickory; Dr. Charles L. Johnson, Jr., Chapel Hill; Dr. Jesse R. Hicks, Charlotte; Dr. Presley Z. Dunn, Jr., and Dr. George Morgan Eckley, both of Statesville; Dr. Tiffany N. Barnes, Asheboro; Dr. Thomas R. Bass, Clayton; and Dr. James H. McCallum, Jr., Williamston.

New officers of the Medical Society of the State of North Carolina include: Dr. Claude B. Squires, Charlotte, President; Dr. John R. Kernodle, Burlington, President-Elect; Dr. John A. Payne III, Sunbury, First Vice-President; Dr. J. Samuel Holbrook, Statesville, Second Vice-President; Dr. John S. Rhodes, Raleigh, Secretary; Dr. Donald B. Koonce, Wilmington, Speaker of the House; and Dr. John C. Reece, Morganton, Vice-Speaker of the House.

Officers of the Medical Alumni Association of the University of North Carolina School of Medicine include Dr. Hugh A. McAllister, Lumberton, President; Dr. Harry Brockmann, High Point, President-Elect; and Dr. A. L. Daughtridge, Rocky Mount, Vice-President.

Dr. Eugene A. Stead, Jr., Chairman of the Duke Medical Center's Department of Medicine, has been elected Secretary of the Association of American Physicians. Dr. James B. Wyngaarden, Professor of Medicine at Duke, was elected a member of the Association.

Dr. Nicholas G. Georgiade, Associate Professor of

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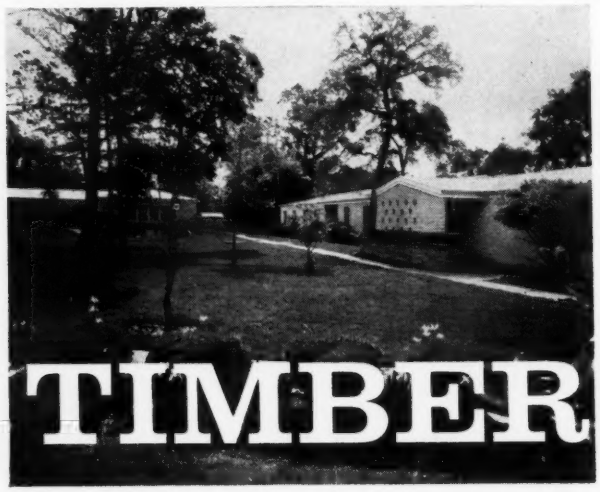

PSYCHIATRIC HOSPITAL

DAY HOSPITAL

DEPARTMENT OF OUT PATIENT PSYCHIATRY

TIMBERLAWN FOUNDATION
For Education and Research in Psychiatry

Narcotic Cases Not Admitted

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RALPH M. BARNETTE, JR., B.B.A., Business Manager

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PHILIP ROOS, PH.D.
DONALD BERTOCH, M.A.
Social Work
BILL M. TURNAGE, M.S.S.W.
ROBERT L. COATES, M.S.S.W.
GERALDINE SKINNER, B.S., O.T.R., Director of Occupational Therapy
LOIS TIMMINS, PH.D., Director of Recreational Therapy
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Concern about changing bacterial sensitivity

Madribon controls even some antibiotic-resistant organisms

Concern about safety and tolerance

Madribon has a safety record unchallenged by any antibacterial agent

Concern about economy and ease of therapy

Madribon is "kind to the purse"; need be given only once a day

Madribon

for respiratory tract infections

Consult literature and dosage information, available on request, before prescribing.

MADRIBON®—2,4-dimethoxy-6-sulfanilamido-1,3-diazine

ROCHE

LABORATORIES • Division of Hoffmann-La Roche Inc.

baby the
infant's skin
with

PANTHODERM® CREAM

relieves itch and pain • promotes healing • guards against irritation and chafing

in 2 oz. and 1 lb. jars,
1 oz. tubes.

IN

DIAPER RASH
EXCORIATED BUTTOCKS
CHAFING, HEAT RASH
INTERTRIGO
ITCHING

Remarkably effective . . . often when other therapy fails . . . Panthoderm Cream treats the infant's skin with "tender, loving care." Clinically it has shown evidence of "epithelizing stimulation . . . an antipruritic effect . . . an antibacterial effect . . . in a variety of dermatoses" such as external ulcers, burns, wounds, pruritus vulvae, a variety of dermatoses. Minimum risk of sensitization.

Dainty as a fine cosmetic, Panthoderm Cream is clean, snow-white, non-staining, water-miscible.

Samples yours for the asking.

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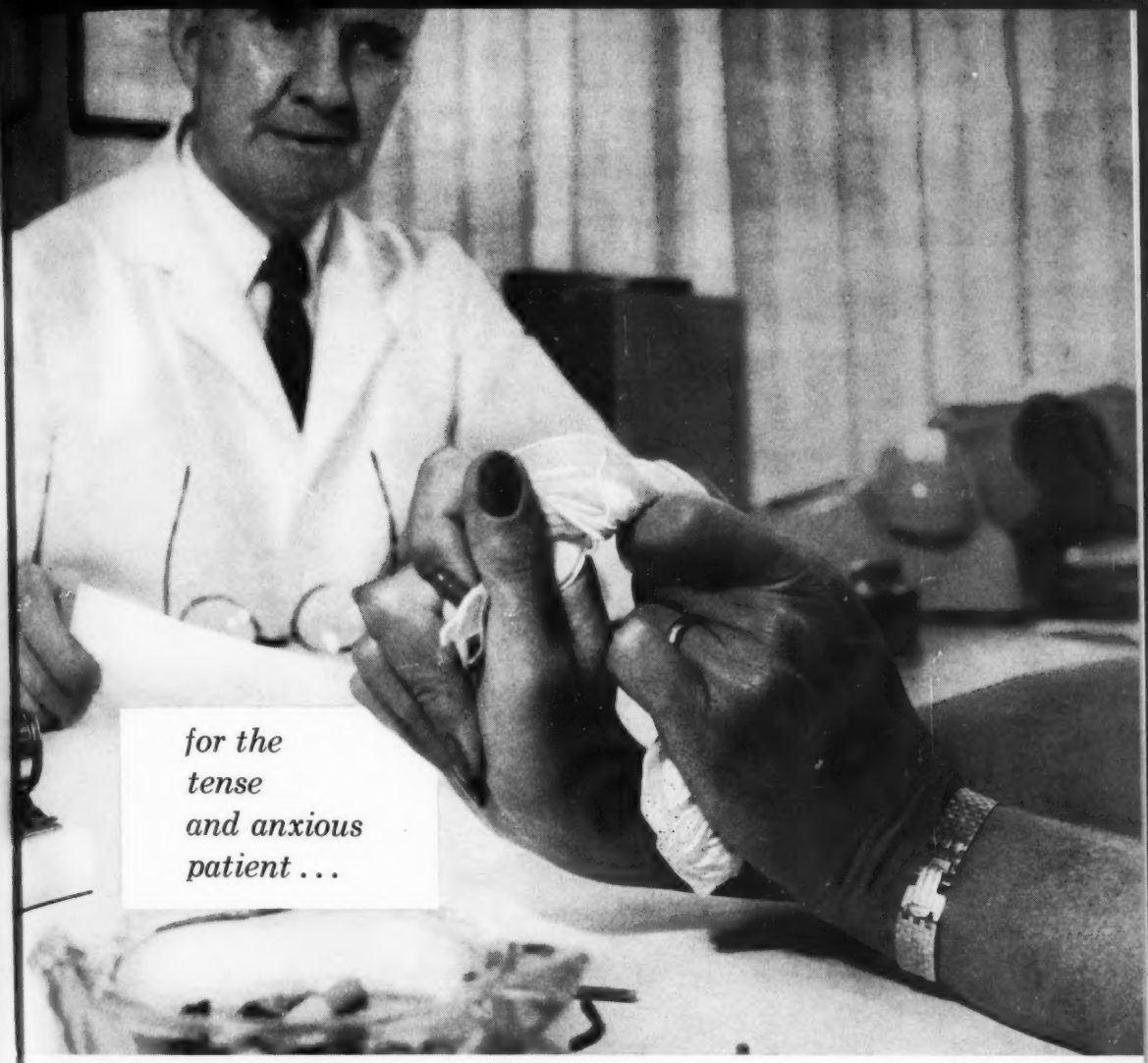
Arlington-Funk Laboratories, division • 250 East 43rd Street, New York 17, N. Y.



the only sustained-release tranquilizer that does not cause autonomic side reactions

- SAFE, CONTINUOUS RELIEF of anxiety and tension for 12 hours with just one capsule—without causing autonomic side reactions and without impairing mental acuity, motor control or normal behavior.
- ECONOMICAL for the patient—daily cost is only a dime or so more than for barbiturates.

Meprospan®-400

400 mg. meprobamate (Miltown®) sustained-release capsules

Usual dosage: One capsule at breakfast lasts all day; one capsule with evening meal lasts all night.

Available: *Meprospan-400*, each blue-topped capsule contains 400 mg. Miltown (meprobamate). *Meprospan-200*, each yellow-topped capsule contains 200 mg. Miltown (meprobamate). Both potencies in bottles of 30.

WALLACE LABORATORIES / *Cranbury, N. J.*

CME-4348

In skeletal muscle spasm

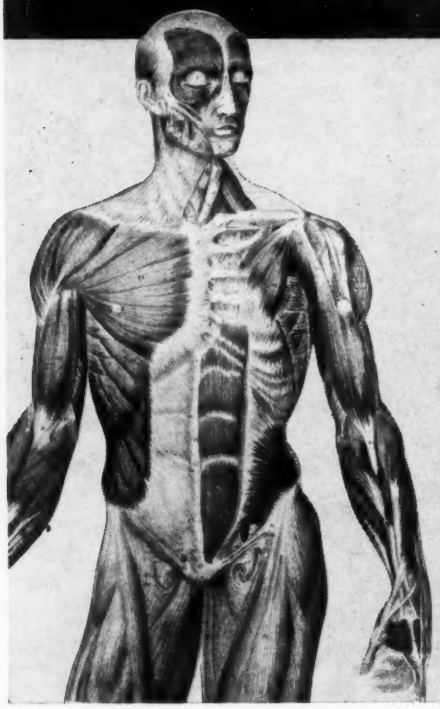
NORFLEX

orphenadrine citrate 100 mg. tablets

quickly resolves the spasm . . .

relieves the pain . . .

restores normal function



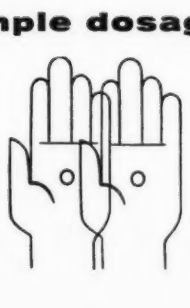
Prolonged relief

may last up to 12 hours after administration . . . permits uninterrupted sleep at night . . . does not interfere with daytime alertness . . . only the muscles in spasm respond . . . no lessening of general muscle tonus.

Contraindications:

Routine precautions against use of anticholinergic drugs should be observed. Norflex should be used with caution in glaucoma, tachycardia, or urinary retention.

Simple dosage



for all adults regardless of age or sex: 2 tablets daily—one in the morning, one in the evening—easily remembered . . . offers better patient cooperation.

NORFLEX is a product of

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*U.S. Patent No. 2,567,351; other patents pending

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POSITIONS AVAILABLE—Positions for Junior and Senior Staff Physicians are available in the state institution for the mentally retarded located across the river from Lynchburg in a most beautiful part of Virginia. Starting salary for those licensed in Virginia is $8,400 to $10,032 depending on qualification. Physicians not licensed in Virginia can be accepted at a salary of $8,040 provided they meet the requirements of the Board of Medical Examiners and have a temporary or permanent ECFMG Certificate. Contact: Dr. Benedict Nagler, Supt., Lynchburg Training School & Hospital, Colony, Virginia.

ANNOUNCEMENT—Fellowship in Gastroenterology—Scott and White Clinic, Scott and White Memorial Hospital and Scott, Sherwood and Brindley Foundation, Temple, Texas. Next appointment available January 1, 1962. For details contact: J. Arnold Bargen, M.D., Scott and White Clinic, Temple, Texas.

WANTED—General Practitioners, interested in Psychiatry. Vacancies exist for several full-time staff physicians. Experience in psychiatry not required. Salaries commensurate with medical training and experience, up to $13,510. Federal fringe benefits. Apply to: Manager, VA Hospital, Augusta, Georgia.

RELOCATION DESIRED—General and Industrial Surgeon desires change in location due to economic

Continued on page 70

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Continued from page 64

Plastic, Maxillofacial and Oral Surgery at Duke University Medical Center, has been chosen to head the American Society of Maxillofacial Surgeons during 1962-1963.

New faculty appointments and promotions at Bowman Gray School of Medicine have been announced by Dr. C. C. Carpenter, Dean of the Medical School. The new appointments are: Dr. Gordon K. Middleton, Instructor in Pediatrics; Dr. Thomas F. O'Brien, Instructor in Medicine; Dr. John M. Pixley, Instructor in Psychiatry; Dr. Paul F. Williams, Instructor in Pre-

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Continued from page 70

ventive Medicine; Dr. Mary Ann Hampton, Assistant in Preventive Medicine; and Dr. Donald C. Hartzog, Assistant in Clinical Medicine. New promotions include: Dr. James F. Martin, from Associate Professor to Professor of Radiology; Dr. Robert W. Prichard, from Associate Professor to Professor of Pathology; Dr. Hugh B. Lofland, from Assistant Professor to Associate Professor of Biochemistry; Dr. Damon D. Blake, from Instructor to Assistant Professor of Radiology; Dr. A. Robert Cordell, from Instructor to Assistant Professor of Surgery; Dr. Donald M. Hayes, from Instructor to Assistant Professor of Medicine; Dr. Richard G. Kessel, from Instructor to Assistant Professor of Anatomy; Dr. J. Stanton King, from Instructor to Research Assistant Professor of Biochemistry; Dr. Malcolm B. McCoy, from Instructor to Assistant Professor of Audiology; Dr. Jesse H. Meredith, from Instructor to Assistant Professor of Surgery; Dr. Benjamin F. Huntley, from Assistant to Instructor in Clinical Medicine; Dr. John H. Nicholson, from Assistant to Instructor in Clinical Medicine; and Dr. William C. Sugg, from Assistant to Instructor in Clinical Medicine.

Dr. Richard Proctor, Associate Professor and Chairman of the Department of Psychiatry at Bowman Gray School of Medicine, has been elected President of the Southeastern Psychiatric Society.

Dr. Frank R. Lock, Winston-Salem, has been elected First Vice-President of the American College of Obstetricians and Gynecologists.

OKLAHOMA

Faculty promotions at the University of Oklahoma School of Medicine include the following full professors: Dr. Robert M. Bird, Medicine; Dr. Merlin K. DuVal, Surgery; and Dr. Charles F. Obermann, Clinical Professor of Psychiatry, Neurology and Behavioral Sciences. All were Associate Professors. Assistant Professors promoted to Associate Professorships were: Drs. Hubert M. Anderson, Rene Menguy, and G. Rainey Williams, Surgery; Drs. Paul C. Benton, Neil B. Kimerer, and Dale W. Peters, Psychiatry; Drs. Richard E. Carpenter, James J. Gable, C. G. Gunn, Robert C. Lawson, Newman S. Matthews, William O. Smith, and Kelly M. West, Medicine; Drs. Glen G. Cayler, Doman K. Keele, and Henry N. Kirkman, Pediatrics; Drs. Edward H. Kalmon, Jr., David D. Lowry, and Hooshang Taybi, Radiology; and Dr. Dick M. Lowry, Otorhinolaryngology. Given the rank of Associate Clinical Professor were: Drs. Charles M. Bielstein, Harold W. Buchner, Louis S. Frank, and Charles W. Freeman, Pediatrics.

Dr. Edward T. Frank has joined the staff of the Oxley-Morgan Clinic in Guymon.

Newly-elected officers of the Oklahoma State Radiological Society are: Dr. E. D. Greenberger, McAlester, President; Dr. G. Ray Ridings, Oklahoma City, Vice-President; Dr. Simon Pollack, Tulsa, Secretary; and Dr. Carl G. Coin, Oklahoma City, Treasurer.

Dr. Malcolm E. Phelps, El Reno, has been re-elected

Continued on page 74

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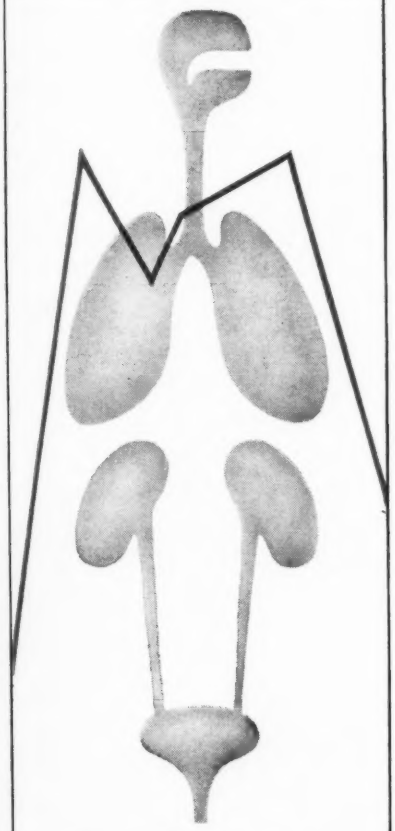

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President of the American Academy of General Practice Foundation Board of Trustees.

SOUTH CAROLINA

Dr. Robert S. Watkins, Camden, has been appointed a member of the Board of Trustees of the State Sanitarium by Governor Hollings.

Dr. C. R. F. Baker, Sumter, has been elected to the Presidency of the South Carolina Surgical Society.

Officers of the South Carolina Association of Public Health physicians include: Dr. M. U. Dantzler, Charleston, President; Dr. Hilla Sheriff, Columbia, Vice-President; and Dr. L. A. Nimmons, Bishopville, Secretary-Treasurer.

Dr. John Tindal Cuttino, acting president of the Medical College of South Carolina, has been awarded the honorary degree of Doctor of Laws by his alma mater, The College of Charleston.

TENNESSEE

Dr. William M. Keeling, Knoxville, has been awarded a Fellowship in the International College of Surgeons.

Dr. William B. Acree, Ridgley, has been named Medical Examiner for Lake County.

Dr. Rudolph M. Landry, Chattanooga, has been elected a Vice-President of the Association of Surgeons of the Southern Railway System.

A member of the County Board of Education of Shelby County is Dr. Jean Hawkes, Memphis.

Dr. David J. Slagle, Elizabethton, has been named President of the Civitan Club.

Dr. Wade Boswell, Knoxville, is President-Elect of the Tennessee Psychiatric Association.

Dr. John M. Hickey, Sevierville, has been elected President of the Optimist Club.

Drs. E. M. Henderson and W. L. Goforth, both of Rogersville, have been elected Chief and Vice-Chief of Staff, respectively, of the Hawkins County Memorial Hospital medical staff.

Dr. Thomas F. Frist, Nashville, has been installed as President of the Middle Tennessee Heart Association.

Dr. H. L. Monroe, Erwin, has accepted the chairmanship of the Unicoi County Red Cross Blood Program.

Dr. James W. Walker, Memphis, has been certified as a Diplomate of the American Board of Plastic and Reconstructive Surgery.

Dr. William Hall Lee, formerly of the University of California Medical Center, has joined the University of Tennessee College of Medicine as Assistant Professor of Surgery.

Dr. Freeman L. Rawson, Knoxville, is President-Elect of the East Tennessee Heart Association and Dr. E. P. Muncy, Jefferson City, is Chairman of the Board.

Officers of the Tennessee Heart Association include: Dr. Joseph E. Acker, Knoxville, President; and Dr. David McCallie, Chattanooga, President-Elect.

Dr. Hugh W. Rule, Kingsport, has been elected to the Board of Mayor and Aldermen of Kingsport.

Dr. Harold G. Sibold, Chattanooga, has been certified

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The Blount Memorial Hospital staff officers are: Dr. T. G. Proctor, Chief of Staff; Dr. C. B. Lequire, Vice-Chief of Staff; Dr. C. B. Howard, Secretary-Treasurer; Dr. W. C. Crowder, Chief of Medicine; and Dr. J. A. Yarborough, Chief of Surgery. All the physicians are from the Maryville-Alcoa area.

Dr. Robert M. Foote, Nashville, and Dr. Bruce Wallas, Memphis, have been elevated to Fellowship in the American Psychiatric Association.

Dr. Sam L. Raines, Memphis, has been re-elected Secretary of the American Urological Association.

Dr. George William Farris, Chattanooga, has been certified as a Diplomate of the American Board of Anesthesiology.

TEXAS

The University of Texas Postgraduate School of Medicine, Temple Division, will present "An Educational Afternoon" on Saturday, Sept. 9, 1961, in Temple. There is no registration fee and the program has been accepted for 3 hours of Category I credit by the American Academy of General Practice. More complete details may be obtained from Dr. R. D. Hines, Chairman, Education and Research Division, Scott and White Clinic, Temple, Texas.

Dr. Milford O. Rouse, Dallas, a Past President of Southern Medical Association, has been re-elected Vice-Speaker of the House of the American Medical Association.

Among the officers of The Society of Nuclear Medicine are Dr. J. R. Maxfield, Jr., Dallas, President-Elect; and Dr. Herbert C. Allen, Jr., Houston, Vice-President. Dr. Maxfield has also been elected to the Board of Trustees of the Episcopal Radio-TV Foundation.

Dr. Louis N. Wilcox, Hughes Springs, is President-Elect of the Cass-Marion County Medical Society.

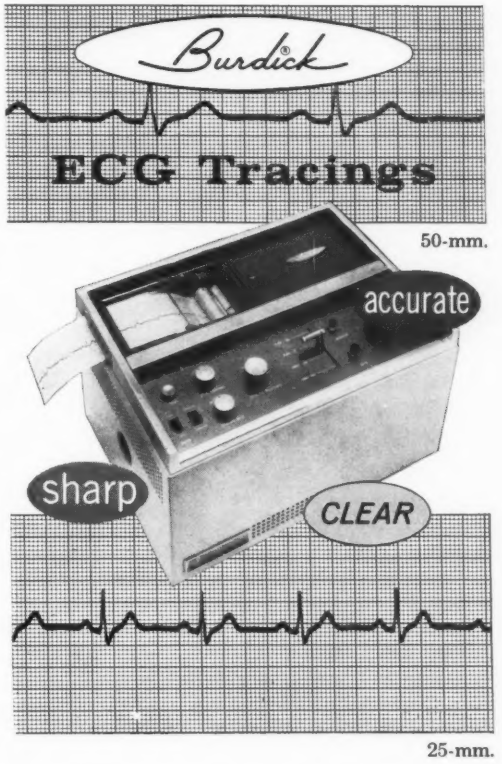
VIRGINIA

Officers of the Virginia Academy of General Practice include: Dr. William J. Hagood, Clover, President; Dr. Harry M. Friden, Norfolk, President-Elect; Dr. Frank D. Daniel, Charlottesville, Vice-President; Dr. Samuel F. Driver, Roanoke, Secretary; and Dr. Irwin Rifkin, Secretary.

Dr. Edgar Childrey, Jr., Richmond, is President of the Virginia Society of Ophthalmology and Otolaryngology. Other officers include Dr. Carl C. Cooley, Norfolk, President-Elect; Dr. A. R. Gillespie, Staunton, Vice-President; and Dr. Marion K. Humphries, Jr., Charlottesville, Secretary-Treasurer.

Dr. Gerald B. Odell, formerly Assistant Professor of Pediatrics at Johns Hopkins University Medical School, is now Chairman of the Pediatrics Department at the Medical College of Virginia.

New members of The Medical Society of Virginia are: Drs. Walter G. Bullington, Richard G. Lester, Sami I. Said, James A. Selph, Jr., and James W. Tinsley III, all of Richmond; Dr. Mehmet S. Akaydin, Marion; Dr. Frederick W. Deck, Fairfax; Dr. Ira D. Godwin, Annandale; Dr. Philip S. Grant, Staunton; and Dr. Joseph D. Vidarte, Portsmouth.



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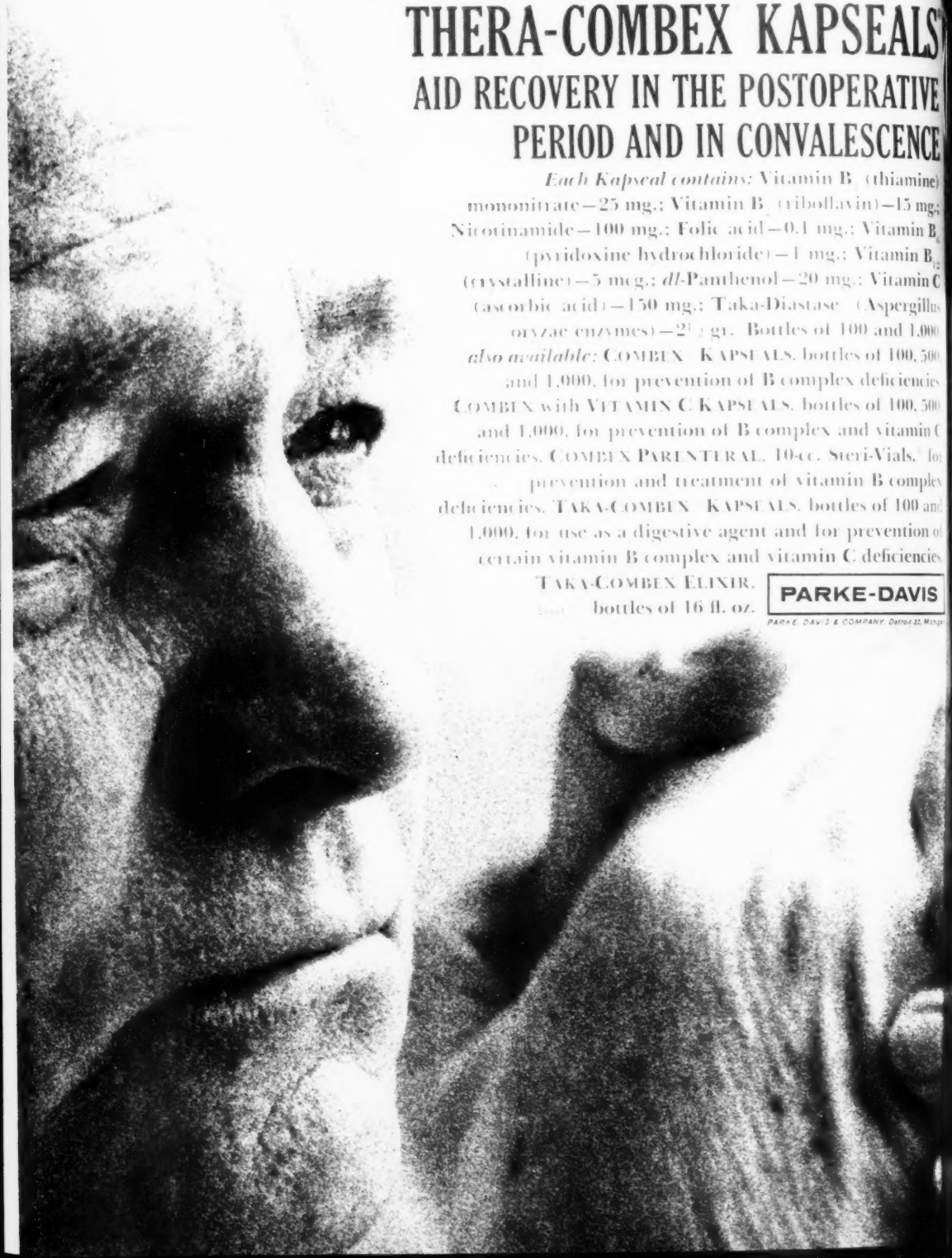

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